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(54) Title: IL-17 RECEPTOR

(57) Abstract

Isolated receptors for IL-17, DNA's encoding such receptors, and pharmaceutical compositions made therefrom, are disclosed. The isolated receptors can be used to regulate an immune response.

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TITLE

## IL-17 RECEPTOR

TECHNICAL FIELD OF THE INVENTION

5       The present invention relates generally to the field of cytokine receptors, and more specifically to cytokine receptor proteins having immunoregulatory activity.

BACKGROUND OF THE INVENTION

Cytokines are hormone-like molecules that regulate various aspects of an immune or inflammatory response. Cytokines exert their effects by specifically binding receptors  
10      present on cells, and transducing a signal to the cells. Rouvier et al. (*J. Immunol.* 150:5445; 1993) reported a novel cDNA which they termed CTLA-8. The putative CTLA8 protein is 57% homologous to the predicted amino acid sequence of an open reading frame (ORF) present in *Herpesvirus saimiri* (HSV) referred to as HVS13 (Nicholas et al. *Virol.* 179:1 89, 1990; Albrecht et al., *J. Virol.* 66:5047;1992). However, the function, if any of  
15      either CTLA-8 or HVS13 was not known, nor was a receptor or binding protein for CTLA-8 or HVS13 known. Thus, prior to the present invention, there was a need in the art to determine the function of CTLA-8 and HVS13, and to identify receptor molecules or binding proteins that play a role in the function of these proteins.

20       SUMMARY OF THE INVENTION

The present invention identifies a novel receptor that binds IL-17 (CTLA-8) and HVS13, a viral homolog of IL-17; DNAs encoding the novel receptor and novel receptor proteins are provided. The receptor is a Type I transmembrane protein; the mouse receptor has 864 amino acid residues, the human receptor has 866 amino acid residues. Soluble forms of the receptor can be prepared and used to regulate immune responses in a therapeutic setting; accordingly, pharmaceutical compositions comprising soluble forms of the novel receptor are also provided. Deleted forms and fusion proteins comprising the novel receptor, and homologs thereof are also disclosed. Also provided are methods of regulating an immune response, and methods of suppressing rejection of grafted organs or  
25      tissue. These and other aspects of the present invention will become evident upon reference to the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

A soluble IL-17 (CTLA-8) protein and an ORF present in *Herpesvirus saimiri* (HVS13) were expressed as fusion proteins comprising an immunoglobulin Fc region, and used to screen cells for expression of a receptor for IL-17. T cell thymoma EL4 cells were  
30

found to bind the HVS13/Fc as well as murine CTLA8 (IL-17)/Fc fusion protein. A cDNA library from EL4 cells was prepared and screened for expression of the receptor. The receptor is a Type I transmembrane protein with 864 amino acid residues, which is referred to as IL-17R (CTLA-8R). Various forms of IL-17R were prepared, including IL-17R/Fc 5 protein, a soluble IL-17R which contains the signal peptide and extracellular domain of IL-17R, and a soluble IL-17R/Flag® construct. A human IL-17R was isolated from a human peripheral blood lymphocyte library by cross-species hybridization, and exhibits similarities to the murine IL-17R. Oligonucleotide probes and primers are also disclosed.

10 **IL-17, HVS13 and homologous proteins**

CTLA-8 refers to a cDNA cloned from an activated T cell hybridoma clone (Rouvier et al., *J. Immunol.* 150:5445; 1993). Northern blot analysis indicated that CTLA-8 transcription was very tissue specific. The CTLA-8 gene was found to map at chromosomal site 1a in mice, and at 2q31 in humans. Although a protein encoded by the 15 CTLA-8 gene was never identified by Rouvier et al, the predicted amino acid sequence of CTLA-8 was found to be 57% homologous to the predicted amino acid sequence of an ORF present in Herpesvirus Saimiri, HVS13. The CTLA-8 protein is referred to herein as Interleukin-17 (IL-17).

The complete nucleotide sequence of the genome of HVS has been reported 20 (Albrecht et al., *J. Virol.* 66:5047; 1992). Additional studies on one of the HVS open reading frames (ORFs), HVS13, are described in Nicholas et al., *Virol.* 179:1 89; 1990. HVS13 is a late gene which is present in the Hind III-G fragment of HVS. Antisera developed against peptides derived from HVS13 are believed to react with a late protein (Nicholas et al., *supra*).

25 As described USSN 08/462,353, a CIP of USSN 08/410,536, filed March 23, 1995, full length murine CTLA-8 protein and a CTLA-8/Fc fusion protein were expressed, tested, and found to act as a costimulus for the proliferation of T cells. Human IL-17 (CTLA-8) was identified by probing a human T cell library using a DNA fragment derived from degenerate PCR; homologs of IL-17 (CTLA-8) are expected to exist in other species 30 as well. A full length HVS13 protein, as well as an HVS13/Fc fusion protein, were also expressed, and found to act in a similar manner to IL-17 (CTLA-8) protein. Moreover, other species of herpesviruses are also likely to encode proteins homologous to that encoded by HVS13.

35 **Proteins and Analogs**

The present invention provides isolated IL-17R and homologs thereof having immunoregulatory activity. Such proteins are substantially free of contaminating

endogenous materials and, optionally, without associated native-pattern glycosylation. Derivatives of IL-17R within the scope of the invention also include various structural forms of the primary protein which retain biological activity. Due to the presence of ionizable amino and carboxyl groups, for example, an IL-17R protein may be in the form of acidic or basic salts, or may be in neutral form. Individual amino acid residues may also be modified by oxidation or reduction.

5 The primary amino acid structure may be modified by forming covalent or aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like, or by creating amino acid sequence mutants.

10 10 Covalent derivatives are prepared by linking particular functional groups to amino acid side chains or at the N- or C-termini.

Soluble forms of IL-17R are also within the scope of the invention. The nucleotide and predicted amino acid sequence of the murine IL-17R is shown in SEQ ID NOs:1 and 2. Computer analysis indicated that the protein has an N-terminal signal peptide with a 15 cleavage site between amino acid 31 and 32. Those skilled in the art will recognize that the actual cleavage site may be different than that predicted by computer analysis. Thus, the N-terminal amino acid of the cleaved peptide is expected to be within about five amino acids on either side of the predicted cleavage site. The signal peptide is followed by a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 521 amino acid 20 cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 322 of SEQ ID NO:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for residues 1 through 31 of SEQ ID NO:1.

The nucleotide and predicted amino acid sequence of the human IL-17R is shown in SEQ ID NOs:9 and 10. It shares many features with the murine IL-17 R. Computer 25 analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 27 and 28. Those skilled in the art will recognize that the actual cleavage site may be different than that predicted by computer analysis. Thus, the N-terminal amino acid of the cleaved peptide is expected to be within about five amino acids on either side of the predicted cleavage site. The signal peptide is followed by a 293 amino 30 acid extracellular domain, a 21 amino acid transmembrane domain, and a 525 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 320 of SEQ ID NO:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for the native signal peptide.

Other derivatives of the IL-17R protein and homologs thereof within the scope of 35 this invention include covalent or aggregative conjugates of the protein or its fragments with other proteins or polypeptides, such as by synthesis in recombinant culture as N-terminal or C-terminal fusions. For example, the conjugated peptide may be a signal (or

leader) polypeptide sequence at the N-terminal region of the protein which co-translationally or post-translationally directs transfer of the protein from its site of synthesis to its site of function inside or outside of the cell membrane or wall (e.g., the yeast  $\alpha$ -factor leader).

5        Protein fusions can comprise peptides added to facilitate purification or identification of IL-17R proteins and homologs (e.g., poly-His). The amino acid sequence of the inventive proteins can also be linked to an identification peptide such as that described by Hopp et al., *BioTechnology* 6:1204 (1988). Such a highly antigenic peptide provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid  
10      assay and facile purification of expressed recombinant protein. The sequence of Hopp et al. is also specifically cleaved by bovine mucosal enterokinase, allowing removal of the peptide from the purified protein. Fusion proteins capped with such peptides may also be  
15      resistant to intracellular degradation in *E. coli*.

15      Fusion proteins further comprise the amino acid sequence of a IL-17R linked to an immunoglobulin Fc region. An exemplary Fc region is a human IgG1 having a nucleotide and amino acid sequence set forth in SEQ ID NO:4. Fragments of an Fc region may also be used, as can Fc muteins such as those described in USSN 08/145,830, filed October 29, 1993. Depending on the portion of the Fc region used, a fusion protein may be expressed as a dimer, through formation of interchain disulfide bonds. If the fusion  
20      proteins are made with both heavy and light chains of an antibody, it is possible to form a protein oligomer with as many as four IL-17R regions.

25      In another embodiment, IL-17R and homologs thereof further comprise an oligomerizing zipper domain. Zipper domains are described in USSN 08/107,353, filed August 13, 1993, the relevant disclosure of which is incorporated by reference herein.  
30      Examples of leucine zipper domains are those found in the yeast transcription factor GCN4 and a heat-stable DNA-binding protein found in rat liver (C/EBP; Landschulz et al., *Science* 243:1681, 1989), the nuclear transforming proteins, *fos* and *jun*, which preferentially form a heterodimer (O'Shea et al., *Science* 245:646, 1989; Turner and Tjian, *Science* 243:1689, 1989), and the gene product of the murine proto-oncogene, *c-myc* (Landschulz et al., *Science* 240:1759, 1988). The fusogenic proteins of several different viruses, including paramyxovirus, coronavirus, measles virus and many retroviruses, also possess leucine zipper domains (Buckland and Wild, *Nature* 338:547, 1989; Britton, *Nature* 353:394, 1991; Delwart and Mosialos, *AIDS Research and Human Retroviruses* 6:703, 1990).

35      Derivatives of IL-17R may also be used as immunogens, reagents in *in vitro* assays, or as binding agents for affinity purification procedures. Such derivatives may also be obtained by cross-linking agents, such as M-maleimidobenzoyl succinimide ester and N-

hydroxysuccinimide, at cysteine and lysine residues. The inventive proteins may also be covalently bound through reactive side groups to various insoluble substrates, such as cyanogen bromide-activated, bisoxirane-activated, carbonyldiimidazole-activated or tosyl-activated agarose structures, or by adsorbing to polyolefin surfaces (with or without 5 glutaraldehyde cross-linking). Once bound to a substrate, proteins may be used to selectively bind (for purposes of assay or purification) antibodies raised against the IL-17R or against other proteins which are similar to the IL-17R, as well as other proteins that bind IL-17R or its homologous proteins.

The present invention also includes IL-17R with or without associated native-pattern glycosylation. Proteins expressed in yeast or mammalian expression systems, e.g., COS-7 cells, may be similar or slightly different in molecular weight and glycosylation pattern than the native molecules, depending upon the expression system. Expression of DNAs encoding the inventive proteins in bacteria such as *E. coli* provides non-glycosylated molecules. Functional mutant analogs of IL-17R protein or homologs thereof having 10 inactivated N-glycosylation sites can be produced by oligonucleotide synthesis and ligation or by site-specific mutagenesis techniques. These analog proteins can be produced in a homogeneous, reduced-carbohydrate form in good yield using yeast expression systems. N-glycosylation sites in eukaryotic proteins are characterized by the amino acid triplet Asn-A<sub>1</sub>-Z, where A<sub>1</sub> is any amino acid except Pro, and Z is Ser or Thr. In this sequence, 15 asparagine provides a side chain amino group for covalent attachment of carbohydrate. Such a site can be eliminated by substituting another amino acid for Asn or for residue Z, deleting Asn or Z, or inserting a non-Z amino acid between A<sub>1</sub> and Z, or an amino acid 20 other than Asn between Asn and A<sub>1</sub>.

IL-17R protein derivatives may also be obtained by mutations of the native IL-17R 25 or its subunits. A IL-17R mutated protein, as referred to herein, is a polypeptide homologous to a IL-17R protein but which has an amino acid sequence different from the native IL-17R because of one or a plurality of deletions, insertions or substitutions. The effect of any mutation made in a DNA encoding a IL-17R peptide may be easily determined by analyzing the ability of the mutated IL-17R peptide to inhibit costimulation of T or B 30 cells by IL-17 (CTLA-8) or homologous proteins, or to bind proteins that specifically bind IL-17R (for example, antibodies or proteins encoded by the CTLA-8 cDNA or the HVS13 ORF). Moreover, activity of IL-17R analogs, muteins or derivatives can be determined by any of the assays methods described herein. Similar mutations may be made in homologs 35 of IL-17R, and tested in a similar manner.

Bioequivalent analogs of the inventive proteins may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine

residues can be deleted or replaced with other amino acids to prevent formation of incorrect intramolecular disulfide bridges upon renaturation. Other approaches to mutagenesis involve modification of adjacent dibasic amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present.

5        Generally, substitutions should be made conservatively; i.e., the most preferred substitute amino acids are those which do not affect the ability of the inventive proteins to bind their ligands in a manner substantially equivalent to that of native mIL-17R or hIL-17R. Examples of conservative substitutions include substitution of amino acids outside of the binding domain(s), and substitution of amino acids that do not alter the secondary  
10      and/or tertiary structure of IL-17R and homologs thereof. Additional examples include substituting one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp; or Gln and Asn. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobicity characteristics, are well known.

15      Similarly, when a deletion or insertion strategy is adopted, the potential effect of the deletion or insertion on biological activity should be considered. Subunits of the inventive proteins may be constructed by deleting terminal or internal residues or sequences. Fragments of IL-17R that bind IL-17 can be readily prepared (for example, by using restriction enzymes to delete portions of the DNA) and tested for their ability to bind IL-17.  
20      Additional guidance as to the types of mutations that can be made is provided by a comparison of the sequence of IL-17R to proteins that have similar structures, as well as by performing structural analysis of the inventive proteins.

Mutations in nucleotide sequences constructed for expression of analog IL-17R (CTLA-8R) must, of course, preserve the reading frame phase of the coding sequences and  
25      preferably will not create complementary regions that could hybridize to produce secondary mRNA structures such as loops or hairpins which would adversely affect translation of the receptor mRNA. Although a mutation site may be predetermined, it is not necessary that the nature of the mutation *per se* be predetermined. For example, in order to select for optimum characteristics of mutants at a given site, random mutagenesis may be conducted  
30      at the target codon and the expressed mutated viral proteins screened for the desired activity.

Not all mutations in the nucleotide sequence which encodes a IL-17R protein or homolog thereof will be expressed in the final product, for example, nucleotide substitutions may be made to enhance expression, primarily to avoid secondary structure  
35      loops in the transcribed mRNA (see EPA 75,444A, incorporated herein by reference), or to provide codons that are more readily translated by the selected host, e.g., the well-known *E. coli* preference codons for *E. coli* expression.

Mutations can be introduced at particular loci by synthesizing oligonucleotides containing a mutant sequence, flanked by restriction sites enabling ligation to fragments of the native sequence. Following ligation, the resulting reconstructed sequence encodes an analog having the desired amino acid insertion, substitution, or deletion.

5        Alternatively, oligonucleotide-directed site-specific mutagenesis procedures can be employed to provide an altered gene having particular codons altered according to the substitution, deletion, or insertion required. Exemplary methods of making the alterations set forth above are disclosed by Walder et al. (*Gene* 42:133, 1986); Bauer et al. (*Gene* 37:73, 1985); Craik (*BioTechniques*, January 1985, 12-19); Smith et al. (*Genetic  
10 Engineering: Principles and Methods*, Plenum Press, 1981); and U.S. Patent Nos. 4,518,584 and 4,737,462 disclose suitable techniques, and are incorporated by reference herein.

15      Due to code degeneracy, there can be considerable variation in nucleotide sequences encoding the same amino acid sequence. Other embodiments include sequences capable of hybridizing under moderately stringent conditions (prewashing solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0) and hybridization conditions of 50°C, 5 X SSC, overnight) to the DNA sequences encoding IL-17R, and other sequences which are degenerate to those which encode the IL-17R. In a preferred embodiment, IL-17R analogs are at least about 70 % identical in amino acid sequence to the amino acid sequence of IL-17R proteins  
20 as set forth in SEQ ID NO:1 or SEQ ID NO:9. Similarly, analogs of IL-17R homologs are at least about 70 % identical in amino acid sequence to the amino acid sequence of the native, homologous proteins. In a most preferred embodiment, analogs of IL-17R or homologs thereof are at least about 80 % identical in amino acid sequence to the native form of the inventive proteins.

25      Percent identity may be determined using a computer program, for example, the GAP computer program described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). For fragments derived from the IL-17R protein, the identity is calculated based on that portion of the IL-17R protein that is present in the fragment. Similar methods can be used to  
30 analyze homologs of IL-17R.

35      The ability of IL-17R analogs to bind CTLA-8 can be determined by testing the ability of the analogs to inhibit IL-17 (CTLA-8)-induced T cell proliferation. Alternatively, suitable assays, for example, an enzyme immunoassay or a dot blot, employing CTLA-8 or HSV13 (or a homolog thereof which binds native IL-17R) can be used to assess the ability of IL-17R analogs to bind CTLA-8. Such methods are well known in the art.

The IL-17R proteins and analogs described herein will have numerous uses, including the preparation of pharmaceutical compositions. The inventive proteins will also

be useful in preparing kits that are used to detect IL-17 or IL-17R, for example, in patient specimens. Such kits will also find uses in detecting the interaction of IL-17 and IL-17R, as is necessary when screening for antagonists or mimetics of this interaction (for example, peptides or small molecules that inhibit or mimic, respectively, the interaction). A variety  
5 of assay formats are useful in such kits, including (but not limited to) ELISA, dot blot, solid phase binding assays (such as those using a biosensor), rapid format assays and bioassays.

#### Expression of Recombinant Receptors for IL-17

10 The proteins of the present invention are preferably produced by recombinant DNA methods by inserting a DNA sequence encoding IL-17R protein or a homolog thereof into a recombinant expression vector and expressing the DNA sequence in a recombinant microbial expression system under conditions promoting expression. DNA sequences encoding the proteins provided by this invention can be assembled from cDNA fragments  
15 and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being inserted in a recombinant expression vector and expressed in a recombinant transcriptional unit.

Recombinant expression vectors include synthetic or cDNA-derived DNA fragments encoding IL-17R, homologs, or bioequivalent analogs, operably linked to  
20 suitable transcriptional or translational regulatory elements derived from mammalian, microbial, viral or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences which control the termination of transcription and translation, as described in detail below. The ability to replicate in a host,  
25 usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants may additionally be incorporated.

DNA regions are operably linked when they are functionally related to each other. For example, DNA for a signal peptide (secretory leader) is operably linked to DNA for a polypeptide if it is expressed as a precursor which participates in the secretion of the  
30 polypeptide; a promoter is operably linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to permit translation. Generally, operably linked means contiguous and, in the case of secretory leaders, contiguous and in reading frame. DNA sequences encoding IL-17R or homologs which are to be expressed in a microorganism  
35 will preferably contain no introns that could prematurely terminate transcription of DNA into mRNA.

Useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and pGEM1 (Promega Biotec, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. *E. coli* is typically transformed using derivatives of pBR322, a plasmid derived from an *E. coli* species (Bolivar et al., *Gene* 2:95, 1977). pBR322 contains genes for ampicillin and tetracycline resistance and thus provides simple means for identifying 10 transformed cells.

Promoters commonly used in recombinant microbial expression vectors include the β-lactamase (penicillinase) and lactose promoter system (Chang et al., *Nature* 275:615, 1978; and Goeddel et al., *Nature* 281:544, 1979), the tryptophan (trp) promoter system (Goeddel et al., *Nucl. Acids Res.* 8:4057, 1980; and EPA 36,776) and tac promoter 15 (Maniatis, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, p. 412, 1982). A particularly useful bacterial expression system employs the phage λ PL promoter and cl857ts thermolabile repressor. Plasmid vectors available from the American Type Culture Collection which incorporate derivatives of the λ PL promoter include plasmid pHUB2, resident in *E. coli* strain JMB9 (ATCC 37092) and pPLc28, resident in 20 *E. coli* RR1 (ATCC 53082).

Suitable promoter sequences in yeast vectors include the promoters for metallothionein, 3-phosphoglycerate kinase (Hitzeman et al., *J. Biol. Chem.* 255:2073, 1980) or other glycolytic enzymes (Hess et al., *J. Adv. Enzyme Reg.* 7:149, 1968; and Holland et al., *Biochem.* 17:4900, 1978), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase. Suitable vectors and promoters for use in yeast expression are further described in R. Hitzeman et al., EPA 73,657.

Preferred yeast vectors can be assembled using DNA sequences from pBR322 for 30 selection and replication in *E. coli* (Amp<sup>R</sup> gene and origin of replication) and yeast DNA sequences including a glucose-repressible ADH2 promoter and α-factor secretion leader. The ADH2 promoter has been described by Russell et al. (*J. Biol. Chem.* 258:2674, 1982) and Beier et al. (*Nature* 300:724, 1982). The yeast α-factor leader, which directs secretion of heterologous proteins, can be inserted between the promoter and the structural gene to be 35 expressed. See, e.g., Kurjan et al., *Cell* 30:933, 1982; and Bitter et al., *Proc. Natl. Acad. Sci. USA* 81:5330, 1984. The leader sequence may be modified to contain, near its 3'

end, one or more useful restriction sites to facilitate fusion of the leader sequence to foreign genes.

The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells may be provided by viral sources. For example, 5 commonly used promoters and enhancers are derived from Polyoma, Adenovirus 2, Simian Virus 40 (SV40), and human cytomegalovirus. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early and late promoter, enhancer, splice, and polyadenylation sites may be used to provide the other genetic elements required for expression of a heterologous DNA sequence. The early and late promoters are particularly 10 useful because both are obtained easily from the virus as a fragment which also contains the SV40 viral origin of replication (Fiers et al., *Nature* 273:113, 1978). Smaller or larger SV40 fragments may also be used, provided the approximately 250 bp sequence extending from the *Hind* III site toward the *Bgl* II site located in the viral origin of replication is included. Further, viral genomic promoter, control and/or signal sequences may be 15 utilized, provided such control sequences are compatible with the host cell chosen. Exemplary vectors can be constructed as disclosed by Okayama and Berg (*Mol. Cell. Biol.* 3:280, 1983).

A useful system for stable high level expression of mammalian receptor cDNAs in C127 murine mammary epithelial cells can be constructed substantially as described by 20 Cosman et al. (*Mol. Immunol.* 23:935, 1986). A preferred eukaryotic vector for expression of IL-17R DNA is referred to as pDC406 (McMahan et al., *EMBO J.* 10:2821, 1991), and includes regulatory sequences derived from SV40, human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV). Other preferred vectors include pDC409 and pDC410, which are derived from pDC406. pDC410 was derived from pDC406 by 25 substituting the EBV origin of replication with sequences encoding the SV40 large T antigen. pDC409 differs from pDC406 in that a *Bgl* II restriction site outside of the multiple cloning site has been deleted, making the *Bgl* II site within the multiple cloning site unique.

A useful cell line that allows for episomal replication of expression vectors, such as 30 pDC406 and pDC409, which contain the EBV origin of replication, is CV-1/EBNA (ATCC CRL 10478). The CV-1/EBNA cell line was derived by transfection of the CV-1 cell line with a gene encoding Epstein-Barr virus nuclear antigen-1 (EBNA-1) and constitutively express EBNA-1 driven from human CMV immediate-early enhancer/promoter.

35 **Host Cells**

Transformed host cells are cells which have been transformed or transfected with expression vectors constructed using recombinant DNA techniques and which contain

sequences encoding the proteins of the present invention. Transformed host cells may express the desired protein (IL-17R or homologs thereof), but host cells transformed for purposes of cloning or amplifying the inventive DNA do not need to express the protein. Expressed proteins will preferably be secreted into the culture supernatant, depending on 5 the DNA selected, but may be deposited in the cell membrane.

Suitable host cells for expression of viral proteins include prokaryotes, yeast or higher eukaryotic cells under the control of appropriate promoters. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or *Bacillus* spp. Higher eukaryotic cells include established cell lines of mammalian origin as described below.

10 Cell-free translation systems could also be employed to produce viral proteins using RNAs derived from the DNA constructs disclosed herein. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (*Cloning Vectors: A Laboratory Manual*, Elsevier, New York, 1985), the relevant disclosure of which is hereby incorporated by reference.

15 Prokaryotic expression hosts may be used for expression of IL-17R or homologs that do not require extensive proteolytic and disulfide processing. Prokaryotic expression vectors generally comprise one or more phenotypic selectable markers, for example a gene encoding proteins conferring antibiotic resistance or supplying an autotrophic requirement, and an origin of replication recognized by the host to ensure amplification within the host.

20 Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium*, and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, although others may also be employed as a matter of choice.

Recombinant IL-17R may also be expressed in yeast hosts, preferably from the *Saccharomyces* species, such as *S. cerevisiae*. Yeast of other genera, such as *Pichia* or 25 *Kluyveromyces* may also be employed. Yeast vectors will generally contain an origin of replication from the 2 $\mu$  yeast plasmid or an autonomously replicating sequence (ARS), promoter, DNA encoding the viral protein, sequences for polyadenylation and transcription termination and a selection gene. Preferably, yeast vectors will include an origin of replication and selectable marker permitting transformation of both yeast and *E. coli*, e.g., 30 the ampicillin resistance gene of *E. coli* and *S. cerevisiae* trp1 gene, which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, and a promoter derived from a highly expressed yeast gene to induce transcription of a structural sequence downstream. The presence of the trp1 lesion in the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of 35 tryptophan.

Suitable yeast transformation protocols are known to those of skill in the art; an exemplary technique is described by Hinnen et al., *Proc. Natl. Acad. Sci. USA* 75:1929,

1978, selecting for  $\text{Trp}^+$  transformants in a selective medium consisting of 0.67% yeast nitrogen base, 0.5% casamino acids, 2% glucose, 10  $\mu\text{g}/\text{ml}$  adenine and 20  $\mu\text{g}/\text{ml}$  uracil. Host strains transformed by vectors comprising the ADH2 promoter may be grown for expression in a rich medium consisting of 1% yeast extract, 2% peptone, and 1% glucose supplemented with 80  $\mu\text{g}/\text{ml}$  adenine and 80  $\mu\text{g}/\text{ml}$  uracil. Derepression of the ADH2 promoter occurs upon exhaustion of medium glucose. Crude yeast supernatants are harvested by filtration and held at 4°C prior to further purification.

Various mammalian or insect cell culture systems can be employed to express recombinant protein. Baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, *Bio/Technology* 6:47 (1988). Examples of suitable mammalian host cell lines include the COS-7 lines of monkey kidney cells, described by Gluzman (*Cell* 23:175, 1981), and other cell lines capable of expressing an appropriate vector including, for example, CV-1/EBNA (ATCC CRL 10478), L cells, C127, 3T3, Chinese hamster ovary (CHO), HeLa and BHK cell lines. Mammalian expression vectors may comprise nontranscribed elements such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, and other 5' or 3' flanking nontranscribed sequences, and 5' or 3' nontranslated sequences, such as necessary ribosome binding sites, a polyadenylation site, splice donor and acceptor sites, and transcriptional termination sequences.

20

#### Purification of Receptors for IL-17

Purified IL-17R, homologs, or analogs are prepared by culturing suitable host/vector systems to express the recombinant translation products of the DNAs of the present invention, which are then purified from culture media or cell extracts. For example, supernatants from systems which secrete recombinant protein into culture media can be first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit.

Following the concentration step, the concentrate can be applied to a suitable purification matrix. For example, a suitable affinity matrix can comprise a counter structure protein or lectin or antibody molecule bound to a suitable support. Alternatively, an anion exchange resin can be employed, for example, a matrix or substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose or other types commonly employed in protein purification. Alternatively, a cation exchange step can be employed. Suitable cation exchangers include various insoluble matrices comprising sulfopropyl or carboxymethyl groups. Sulfopropyl groups are preferred. Gel filtration chromatography also provides a means of purifying the inventive proteins.

Affinity chromatography is a particularly preferred method of purifying IL-17R and homologs thereof. For example, a IL-17R expressed as a fusion protein comprising an immunoglobulin Fc region can be purified using Protein A or Protein G affinity chromatography. Moreover, a IL-17R protein comprising an oligomerizing zipper domain

5 may be purified on a resin comprising an antibody specific to the oligomerizing zipper domain. Monoclonal antibodies against the IL-17R protein may also be useful in affinity chromatography purification, by utilizing methods that are well-known in the art. A ligand (i.e., IL-17 or HVS-13) may also be used to prepare an affinity matrix for affinity purification of IL-17R.

10 Finally, one or more reversed-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify a IL-17R composition. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a homogeneous recombinant protein.

15 Recombinant protein produced in bacterial culture is usually isolated by initial extraction from cell pellets, followed by one or more concentration, salting-out, aqueous ion exchange or size exclusion chromatography steps. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of recombinant viral protein can be disrupted by any convenient

20 method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Fermentation of yeast which express the inventive protein as a secreted protein greatly simplifies purification. Secreted recombinant protein resulting from a large-scale fermentation can be purified by methods analogous to those disclosed by Urdal et al. (*J. Chromatog.* 296:171, 1984). This reference describes two sequential, reversed-phase HPLC steps for purification of recombinant human GM-CSF on a preparative HPLC column.

25 Protein synthesized in recombinant culture is characterized by the presence of cell components, including proteins, in amounts and of a character which depend upon the

30 purification steps taken to recover the inventive protein from the culture. These components ordinarily will be of yeast, prokaryotic or non-human higher eukaryotic origin and preferably are present in innocuous contaminant quantities, on the order of less than about 1 percent by weight. Further, recombinant cell culture enables the production of the inventive proteins free of other proteins which may be normally associated with the

35 proteins as they are found in nature in the species of origin.

#### Administration of IL-17R Compositions

The present invention provides methods of using therapeutic compositions comprising an effective amount of a protein and a suitable diluent and carrier, and methods for regulating an immune response. The use of IL-17R or homologs in conjunction with soluble cytokine receptors or cytokines, or other immunoregulatory molecules is also contemplated. Moreover, DNA encoding soluble IL-17R will also be useful; a tissue or organ to be transplanted can be transfected with the DNA by any method known in the art. The organ or tissue thus expresses soluble IL-17R, which acts in the localized area of the graft to suppress rejection of the graft. Similar methods comprising administering such DNA's to the site of the graft will also show efficacy in ameliorating graft rejection.

For therapeutic use, purified protein is administered to a patient, preferably a human, for treatment in a manner appropriate to the indication. Thus, for example, IL-17R protein compositions administered to regulate immune function can be given by bolus injection, continuous infusion, sustained release from implants, or other suitable technique. Typically, a therapeutic agent will be administered in the form of a composition comprising purified IL-17R, in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers will be nontoxic to recipients at the dosages and concentrations employed.

Ordinarily, the preparation of such protein compositions entails combining the inventive protein with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in trials. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

Receptors for IL-17 (CTLA-8) can be administered for the purpose of inhibiting T cell proliferation, or for inhibiting T cell activation. Soluble IL-17R are thus likely to be useful in preventing or treating organ or graft rejection, autoimmune disease, allergy or asthma. The inventive receptor proteins will also be useful for prevention or treatment of inflammatory disease in which activated T cells play a role. Similarly, HVS13 and homologs thereof stimulate B cell proliferation and immunoglobulin secretion; thus, receptors that bind HVS13 or CTLA-8 will be useful *in vivo* to inhibit B cell proliferation or immunoglobulin secretion. Receptors for CTLA-8 will also be useful to inhibit the binding of HVS13 or CTLA-8 to cells expressing IL-17R.

The following examples are offered by way of illustration, and not by way of limitation. Those skilled in the art will recognize that variations of the invention embodied in the examples can be made, especially in light of the teachings of the various references cited herein, the disclosures of which are incorporated by reference.

5

### EXAMPLE 1

This example describes identification of cells that express a receptor (or counterstructure) for HVS13/mCTLA8. A chimeric protein (HVS13 type II Fc) consisting of an Fc region of a human immunoglobulin (SEQ ID NO:4) followed by the amino acid 19 to 151 of HVS 13 (SEQ ID NO:8) was prepared. A murine CTLA8/Fc (mCTLA8/Fc) was constructed by fusing amino acid 22 to 150 of mCTLA8 (SEQ ID NO:6) to the Fc region of human IgG1. A control Fc protein was constructed by a similar method. The HVS13/Fc and mCTLA-8 proteins were expressed and used to identify cell sources by flow cytometry.

Cells ( $1 \times 10^6$ ) were preincubated on ice for 30 minutes in 100  $\mu$ l of FACS buffer (PBS, 1% FCS and 0.1% NaN<sub>3</sub>) containing 2% normal goat serum and 2% normal rabbit serum to block nonspecific binding. 100  $\mu$ l of HVS 13/Fc, mCTLA-8/Fc or control/Fc protein was added at 5  $\mu$ g/ml and incubated on ice for 30 min. After washing, the cells were stained with biotin labeled anti human IgG (Fc specific) followed by PE-conjugated streptavidin (Becton Dickson & Co, Mountain View, CA) in 100  $\mu$ l of FACS buffer. Cells were then washed and analyzed using a FACScan (Becton Dickinson). A minimum of 5,000 cells were analyzed for each sample. More than a dozen cell lines were screened and it was found that both HVS13/Fc and mCTLA8/Fc fusion proteins bound specifically to the murine thymoma cell line EL4. These cells did not bind to the control/Fc fusion protein.

25

### EXAMPLE 2

This example describes cloning of the gene that encodes IL-17R. After identification of a source for HVS13 counterstructure, an EL4 mammalian expression library was screened by a slide-binding autoradiographic method (Gearing et al., *EMBO J.* 8:3667, 1989). CV1/EBNA cells were maintained in Dulbecco's modified Eagle's medium (DMEM) containing 10% (v/v) fetal calf serum (FCS) at 37°C in a humidified atmosphere containing 10% CO<sub>2</sub> and passaged twice weekly. Subconfluent CV1/EBNA cell monolayers on fibronectin-treated chamber slides (Labtek) were transfected by a chloroquine-mediated DEAE-dextran procedure with plasmid DNAs derived from pooled transformants (2,000 transformants per pool) of murine EL4 cDNA library.

The CV1/EBNA cells transfected with the murine EL4 cDNA pools were assayed for HVS13/Fc binding two days after transfection using [<sup>125</sup>I] labeled goat anti-human IgG

binding and slide autoradiography. Transfected cell monolayers were washed with binding medium (RPMI 1640 containing 1% bovine serum albumin and 50 mg/ml non-fat dry milk), then incubated with 1 µg/ml of HVS13/Fc for one hour at room temperature. Cells were washed, incubated with <sup>125</sup>I-labeled goat anti-human IgG (New England nuclear, Cambridge, MA). Cells were washed twice with binding medium, three times with PBS, and fixed in PBS containing 2.5% gluteraldehyde for 30 minutes, washed twice more with PBS and air dried. The chamber slides were then dipped in Kodak GTNB-2 photographic emulsion and exposed for 3 days at 4°C before developing.

Forty pools of approximately 2,000 cDNA each were transfected into CV1/EBNA cells. Two pools of cDNA were found to confer binding to HVS13/Fc protein. These pools were broken down to pools of 100 cDNAs, and subsequently to individual clones. Two single cDNA clones were isolated. These clones were transfected into CV1/EBNA to determine whether the protein encoded thereby conferred binding to both HVS13/Fc and mCTLA8/Fc. Both HVS/Fc and mCTLA8/Fc bound to CV1/EBNA cells transfected with the cloned cDNA, but not to cells transfected with empty vector. Control/Fc did not bind to either of them.

Sequencing of these clones found that they contained a 3.2 kb and 1.7 kb insert derived from same mRNA. The 3.2 kb clone contained an open reading frame of 2595 bp surrounded by 120 bp at the 5' noncoding sequence and 573 bp of 3' noncoding sequence. There were no in-frame stop codons upstream of the predicted initiator methionine, which is preceded by a purine residue (guanine) at -3 position, the most important indicator of a good translation initiation site (Kozak, *Mol. Cell. Biol.* 9:5134, 1989). It also has a guanine at +4 position, making it an optimal for translation initiation. The open reading frame is predicted to encode a type I transmembrane protein of 864 amino acids. The nucleotide and predicted amino acid sequence is shown in SEQ ID NOs:1 and 2.

Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 31 and 32. The signal peptide is followed by a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 521 amino acid cytoplasmic tail. There are eight potential N-linked glycosylation sites in the extracellular domain of the protein. The predicted molecular weight for this protein is 97.8 kilodaltons with an estimated isoelectric point of 4.85. Comparison of both nucleotide and amino acid sequences with the GenBank or EMBL databases found no significant homology with known nucleotide and protein sequences.

In order to determine the cellular and tissue distribution of IL-17R mRNA, poly (A)<sup>+</sup> RNA derived from various murine cell lines or tissues was examined by Northern blot analysis using the IL-17R cDNA as a probe. Filters containing poly(A)<sup>+</sup> RNA (2 µg per lane) from various tissues were purchased from Clontech (Palo Alto, CA).

Polyadenylated RNA from various cells or cell lines were isolated, fractionated (2 µg per lane) on a 1% agarose formaldehyde gel, blotted onto Hybond nylon membrane (Amersham). Filters were probed with an anti-sense RNA riboprobe corresponding to the coding region of IL-17R cDNA. Hybridization was performed at 63°C followed by three washings in 0.2% x SSC, 0.1% SDS at 68°C. Blots were exposed for 8 to 48 hr at -70°C.

The IL-17R probe hybridized to a single species of mRNA of approximately 3.7 kb in all tissues. Among the tissues examined, strong hybridizing signals were observed in spleen and kidney. Moderate signals were observed in lung and liver, and weaker signals in brain, heart, skeletal muscle and testes. Similar size mRNAs were detected in the following cells and cell lines: fetal liver epithelial cells (D11), fibroblast (3T3), rat intestinal epithelial cells (1CE6), splenic B cells, muscle cells (BB4), mast cells (H7), triple negative thymus cells (TN), pre-B cells (70Z/3), T cell hybridoma (EL4); and T cell clones 7C2 and D10. All the cell lines tested were found to express IL-17R mRNA, suggesting a ubiquitous expression of IL-17R message.

#### EXAMPLE 3

This example describes construction of a construct to express a soluble IL-17R/Flag® protein referred to as IL-17R/Flag. IL-17R/Flag® contains a leader sequence, and the region of IL-17R from amino acid 1 to amino acid 322 (SEQ ID NO:1), and the octapeptide referred to as Flag® (SEQ ID NO:3). The construct is prepared essentially as described for other soluble constructs, by ligating a DNA fragment encoding amino acids 1 through 322 of SEQ ID NO:1 (prepared as described in Example 4) into an appropriate expression vector which contains a suitable leader sequence. The resultant DNA construct is transfected into a suitable cell line such as the monkey kidney cell line CV-1/EBNA (ATCC CRL 10478). IL-17R/Flag® may be purified using a Flag® antibody affinity column, and analyzed for biological activity using any of the methods described herein.

#### EXAMPLE 4

This example describes construction of a IL-17R DNA construct to express a IL-17R/Fc fusion protein. A soluble form of IL-17R fused to the Fc region of human IgG1 was constructed in the mammalian expression vector pDC409 in the following way: A pair of oligonucleotide primers containing a sense sequence and an antisense sequence of IL-17R were synthesized. The sense primer contained a Sal I site at the 5' end of the cDNA and antisense primer contained a Bgl II site and contained the IL-17R truncated just before the transmembrane region and a stop codon. A 980 bp DNA fragment was amplified from IL-17R cDNA. The PCR product was cut with Sal I and Bgl II and used in a three way

ligation with a fragment carrying the human IgG1 region cut with Bgl II and Not I into a plasmid (pDC409; see USSN 08/235,397) previously cut with Sal I and Not I. The encoded insert contained the nucleotides encoding the amino acid sequence of residues 1 to 322 of IL-17R (SEQ ID N0:1). The sequence was confirmed by sequencing the whole  
5 region.

The IL-17R/Fc expression plasmids were transfected into CV-1/EBNA cells, and supernatants were collected for 1 week. The CTLA-8/Fc fusion proteins were purified on a protein A sepharose column (Pharmacia, Uppsala, Sweden) as described below. Protein concentration was determined by an enzyme-linked immunoabsorbent assay specific for the  
10 constant domain of human IgG1 and by BCA analysis (Pharmacia), and purity was confirmed by SDS-polyacrylamide gel electrophoresis analysis followed by silver stain of the gel.

#### EXAMPLE 5

This example describes purification of IL-17R fusion proteins. IL-17R/Fc fusion protein is purified by conventional methods using Protein A or Protein G chromatography.  
15 Approximately one liter of culture supernatant containing IL-17R/Fc fusion protein is purified by filtering mammalian cell supernatants (e.g., in a 0.45m filter) and applying filtrate to a protein A/G antibody affinity column (Schleicher and Schuell, Keene, NH) at 4°C at a flow rate of 80 ml/hr for a 1.5 cm x 12.0 cm column. The column is washed with  
20 0.5 M NaCl in PBS until free protein is not detected in the wash buffer. Finally, the column is washed with PBS. Bound fusion protein is eluted from the column with 25 mM citrate buffer, pH 2.8, and brought to pH 7 with 500 mM Hepes buffer, pH 9.1.

A IL-17R fusion protein comprising Flag® may also be detected and/or purified using an antibody that binds Flag®, substantially as described in Hopp et al.,  
25 *BioTechnology* 6:1204 (1988). Biological activity is measured by inhibition of CTLA-8 activity in any biological assay which quantifies the co-stimulatory effect of CTLA-8, for example, as described in the Examples herein.

#### EXAMPLE 6

This example illustrates the preparation of monoclonal antibodies against IL-17R.  
30 Preparations of purified recombinant IL-17R, for example, or transfected cells expressing high levels of IL-17R, are employed to generate monoclonal antibodies against IL-17R using conventional techniques, such as those disclosed in U.S. Patent 4,411,993. Such antibodies are likely to be useful in interfering with IL-17R binding to CTLA-8, as components of diagnostic or research assays for IL-17R, or in affinity purification of IL-  
35 17R.

To immunize rodents, IL-17R immunogen is emulsified in an adjuvant (such as complete or incomplete Freund's adjuvant, alum, or another adjuvant, such as Ribi adjuvant R700 (Ribi, Hamilton, MT), and injected in amounts ranging from 10-100 µg subcutaneously into a selected rodent, for example, BALB/c mice or Lewis rats. Ten days 5 to three weeks later, the immunized animals are boosted with additional immunogen and periodically boosted thereafter on a weekly, biweekly or every third week immunization schedule. Serum samples are periodically taken by retro-orbital bleeding or tail-tip excision for testing by dot-blot assay (antibody sandwich), ELISA (enzyme-linked immunosorbent assay), immunoprecipitation, or other suitable assays, including FACS analysis. Following detection of an appropriate antibody titer, positive animals are given 10 an intravenous injection of antigen in saline. Three to four days later, the animals are sacrificed, splenocytes harvested, and fused to a murine myeloma cell line (e.g., NS1 or preferably Ag 8.653 [ATCC CRL 1580]). Hybridoma cell lines generated by this procedure are plated in multiple microtiter plates in a selective medium (for example, one 15 containing hypoxanthine, aminopterin, and thymidine, or HAT) to inhibit proliferation of non-fused cells, myeloma-myeloma hybrids, and splenocyte-splenocyte hybrids.

Hybridoma clones thus generated can be screened by ELISA for reactivity with IL-17R, for example, by adaptations of the techniques disclosed by Engvall et al., *Immunochem.* 8:871 (1971) and in U.S. Patent 4,703,004. A preferred screening 20 technique is the antibody capture technique described by Beckman et al., *J. Immunol.* 144:4212 (1990). Positive clones are then injected into the peritoneal cavities of syngeneic rodents to produce ascites containing high concentrations (>1 mg/ml) of anti-IL-17R monoclonal antibody. The resulting monoclonal antibody can be purified by ammonium sulfate precipitation followed by gel exclusion chromatography. Alternatively, affinity 25 chromatography based upon binding of antibody to protein A or protein G can also be used, as can affinity chromatography based upon binding to IL-17R protein.

#### EXAMPLE 7

This example illustrates the ability of IL-17R to inhibit the proliferative response of T cells to mitogens. Lymphoid organs were harvested aseptically and cell suspension was 30 created. Splenic and lymph node T cells were isolated from the cell suspension. The purity of the resulting splenic T cell preparations was routinely >95% CD3<sup>+</sup> and <1% sIgM<sup>+</sup>. Purified murine splenic T cells (2x10<sup>5</sup>/well) were cultured with either 1% PHA or 1 µg/ml Con A, and a soluble IL-17R was titrated into the assay. Proliferation was determined after 3 days with the addition of 1 µCi [<sup>3</sup>H]thymidine. Secretion of cytokines 35 (Interleukin-2) was determined for murine T cells cultured for 24 hr with 1 µg/ml of Con A in the presence or absence of 10 µg/ml of IL-17R.Fc or in the presence of a control Fc

protein. IL-2 production was measured by ELISA and results expressed as ng/ml IL-2 produced.

Soluble IL-17R/Fc significantly inhibited the mitogen-induced proliferation of purified murine splenic T cells in a dose dependent manner, while a control Fc had no effect on the murine T cell proliferation. Complete inhibition of mitogen induced proliferation was observed at a soluble IL-17R.Fc concentration of 10 µg/ml. Analysis of IL-2 production by splenic T cells activated with Con A in the presence or absence of IL-17R.Fc in the culture revealed that addition of IL-17R.Fc to the T-cell culture inhibited IL-2 production to levels 8-9-fold lower than those observed in cultures containing media alone or media plus a control Fc protein. Similar results were observed when purified human T cells were used.

#### EXAMPLE 8

This example presents the isolation of a DNA encoding human IL-17R by cross species hybridization. A human peripheral blood lymphocyte library was prepared and screened substantially as described in USSN 08/249,189, using murine IL-17R DNA under moderately high stringency conditions. Several clones of varying length were obtained. Sequencing data indicated that the human IL-17R was approximately 76% identical to murine IL-17R at the nucleotide level. The nucleotide and predicted amino acid sequence of human IL-17R is shown in SEQ ID NOs:10 and 11. A plasmid (pGEMBL) containing DNA encoding the human IL-17 receptor (referred to as pGEMBL-HuIL-17R) in *E. coli* DH10, was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852-1776, USA, on June 5, 1995, under the conditions of the Budapest Treaty, and assigned accession number 69834.

The human IL-17R shared many features with the murine IL-17 R. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 27 and 28. The signal peptide is followed by a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 525 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 320 of SEQ ID N0:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for the native signal peptide. A Type I Fc fusion protein (wherein DNA encoding the Fc region of an immunoglobulin molecule is fused to DNA encoding the IL-17R immediately before, and in place of, the DNA encoding the transmembrane region of the IL-17R) was prepared, substantially as described in Example 4. A soluble hIL-17R protein can be also expressed substantially as described in Example 3, or by any other method of preparing and expressing the extracellular domain of IL-17R or a fragment thereof..

**EXAMPLE 9**

This example presents the localization and fine mapping of the murine IL-17R gene. A panel of DNA samples from an interspecific cross that has been characterized for over 900 genetic markers throughout the genome was analyzed. The genetic markers included in this map span between 50 and 80 centi-Morgans on each mouse autosome and the X chromosome (Chr) (Saunders and Seldin, *Genomics* 8:524, 1990; Watson et al., *Mammalian Genome* 2:158, 1992).

Initially, DNA from the two parental mice [C3H/HeJ-gld and (C3H/HeJ-gld x *Mus spreitus*) F1] were digested with various restriction endonucleases and hybridized with the IL-17R cDNA probe to determine restriction fragment length variants (RFLVs) to allow haplotype analyses. Informative *Bgl*I RFLVs were detected: C3H/HeJ-gld, 10.0 kb; *Mus spreitus*, 7.8 kb and 2.2 kb). In each of the backcross mice either the C3H/HeJ-gld parental band or all three bands (both *Mus spreitus* bands and a half intensity C3H/HEJ-gld band) were observed indicating that a single locus was detected.

Comparison of the haplotype distribution of the IL-17R RFLVs indicated that this gene cosegregated in 111 of the 114 meiotic events examined with the *Raf1* gene locus on mouse Chr 6. The best gene order (Bishop, *Genet. Epidemiol.* 2:349, 1985) ± the standard deviation (Green, In Genetics and Probability in Animal Breeding Experiments. E. Green, ed.; Macmillan, New York, pp.77-113, 1981) was: (centromere) *Raf1*-2.6 cM ± 1.5 cM - *IL-17R* - 2.5 cM ± 1.5 cM - *Cd4*.

**EXAMPLE 10**

This example demonstrates that soluble IL-17R suppresses rejection of organ grafts *in vivo*. Hearts from neonatal C57BL/6 (H-2<sup>b</sup>) mice (less than 24 hours old) were transplanted into the ear pinnae of adult BALB/c (H-2<sup>d</sup>) recipients substantially as described in U.S. patent 5,492,888, issued February 20, 1996 (utilizing the method of Fulmer et al., *Am. J. Anat.* 113:273, 1963, modified as described by Trager et al., *Transplantation* 47:587, 1989, and Van Buren et al., *Transplant. Proc.* 15:2967, 1983). Survival of the transplanted hearts was assessed by visually inspecting the grafts for pulsatile activity, as determined by examining the ear-heart grafts of anesthetized recipients under a dissecting microscope with soft reflected light beginning on day 5 or 6 post transplant. The time of graft rejection was defined as the day after transplantation on which contractile activity ceased.

In one set of experiments, neonatal hearts were removed, rinsed with sterile PBS to remove excess blood, and placed into prepared ear pinnae. Recipient mice were given either soluble murine IL-17R/Fc (100 µg in 200 µl; see Example 4 herein) or rat IgG as a control, i.p. on days 0 through 3 post transplantation. In a second set of experiments, the

recipient mice were injected with IL-17R or human IgG on days 0, 1 and 2; the quantity and route of injection were ass done previously. The results of these experiments are shown in Table 1.

5

Table 1: Effects of Soluble Murine IL-17R (smuIL-17R) on Neovascularized Heterotopic Cardiac Allograft Survival

	Treatment Group	Survival Time (days)	Median Survival Time ± S. D.
Experiment 1	rat IgG	11, 14, 14, 14	13 ± 1.5
	smuIL-17R	19, 19, 19, 21	20 ± 1.0
Experiment 2	human IgG	13, 13, 13, 15	14 ± 1.0
	smuIL-17R	20, 20, 20, 20	20 ± 0.0

Table 1 shows that heart allografts survived approximately 13 days in individual control mice treated with rat IgG. When allograft recipients were given up to four daily 10 injections of soluble IL-17R, graft survival was prolonged, with a median survival of 20, approximately seven days longer than the survival time of identical grafts in control mice. When a prolonged release of the IL-17R was obtained by encapsulating the soluble IL-17R 15 in alginate beads, it was observed that a single administration of 100 µg soluble IL-17R prolonged graft survival in much the same manner as observed previously with soluble IL-17R in solution. These results demonstrate that soluble IL-17R suppresses rejection of grafted tissues.

#### EXAMPLE 11

This example demonstrates that DNA encoding soluble IL-17R will be useful in 20 suppressing rejection of organ grafts *in vivo*. Hearts from neonatal C57BL/6 (H-2<sup>b</sup>) mice were transplanted into the ear pinnae of adult BALB/c (H-2<sup>d</sup>) recipients as described in Example 10 above, except that the hearts were injected with 15 µl of PBS containing either IL-17R/Fc-encoding DNA (pDC409-IL-17R; Example 4) or control DNA (empty pDC409) at a concentration of about 1 mg/ml, into a ventricle. A 30 gauge needle was used, and care 25 was taken to minimize trauma to the heart. The transfected hearts were then transplanted into BALB/c recipients and graft survival determined as described previously. Results are presented in Table 2.

**Table 2: Effects of Expression of Soluble Murine IL-17R by Cardiac Cells on Neovascularized Heterotopic Cardiac Allograft Survival**

Treatment Group	Survival Time (days)	Median Survival Time ± S. D.
rat IgG	13, 15, 15, 15, 18	15 ± 1.8
smuIL-17R	20, 25, 28, >60, >60	ND*

\*ND: Not done; median survival time could not be calculated since two mice still show pulsatile grafts more than two months after transplantation.

5

Table 2 shows that heart allografts survived approximately 15 days in individual control mice transplanted with hearts transfected with empty vector. When the transplanted hearts were transfected with DNA encoding soluble IL-17R, graft survival was prolonged. For three of the five mice in this group, grafts survived on average approximately 24 days, nine days longer than the survival time of identical grafts in control mice. The grafts given the other two mice were still pulsatile (i.e., had not been rejected) more than 60 days post transplant., and had apparently been accepted by the recipients. These results demonstrate that transfecting tissues to be grafted with DNA encoding soluble IL-17R ameliorates rejection of those tissues by the recipient.

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## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

5

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15

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(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: Apple Macintosh  
(C) OPERATING SYSTEM: Apple Operating System 7.1  
(D) SOFTWARE: Microsoft Word for Apple, Version 5.1a

25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:

30

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 08/538,765  
(B) FILING DATE: 07 AUG 1995  
(C) CLASSIFICATION:

35

(viii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 08/410,535  
(B) FILING DATE: 23 MAR 1995  
(C) CLASSIFICATION:

40

(ix) ATTORNEY/AGENT INFORMATION:

(A) NAME: Perkins, Patricia Anne  
(B) REGISTRATION NUMBER: 34,695  
(C) REFERENCE/DOCKET NUMBER: 2617-WO

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(x) TELECOMMUNICATION INFORMATION:

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(A) TELEPHONE: (206)587-0430  
(B) TELEFAX: (206)

## (2) INFORMATION FOR SEQ ID NO:1:

55

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3288 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single

## (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

5 (iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

10 (vi) ORIGINAL SOURCE:

(A) ORGANISM: Mouse

(B) CLONE: HVS13 receptor

(ix) FEATURE:

(A) NAME/KEY: CDS

15 (B) LOCATION: 121..2715

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

20	GTCGACTGGA ACGAGACGAC CTGCTGCCGA CGAGCGCCAG TCCTCGGCCG GGAAAGCCAT	60
	CGCGGGCCCT CGCTGTCGCG CGGAGCCAGC TGCGAGCGCT CCGCGACCAG GCGAGGGCT	120
25	ATG GCG ATT CGG CGC TGC TGG CCA CGG GTC GTC CCC GGG CCC GCG CTG	168
	Met Ala Ile Arg Arg Cys Trp Pro Arg Val Val Pro Gly Pro Ala Leu	
	1 5 10 15	
	GGA TGG CTG CTT CTG CTG CTG AAC GTT CTG GCC CCG GGC CGC GCC TCC	216
30	Gly Trp Leu Leu Leu Leu Asn Val Leu Ala Pro Gly Arg Ala Ser	
	20 25 30	
	CCG CGC CTC CTC GAC TTC CCG GCT CCG GTC TGC GCG CAG GAG GGG CTG	264
	Pro Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu	
	35 40 45	
35	AGC TGC AGA GTC AAG AAT AGT ACT TGT CTG GAT GAC AGC TGG ATC CAC	312
	Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His	
	50 55 60	
40	CCC AAA AAC CTG ACC CCG TCT TCC CCA AAA AAC ATC TAT ATC AAT CTT	360
	Pro Lys Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu	
	65 70 75 80	
45	AGT GTT TCC TCT ACC CAG CAC GGA GAA TTA GTC CCT GTG TTG CAT GTT	408
	Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val	
	85 90 95	
	GAG TGG ACC CTG CAG ACA GAT GCC AGC ATC CTG TAC CTC GAG GGT GCA	456
50	Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala	
	100 105 110	
	GAG CTG TCC GTC CTG CAG CTG AAC ACC AAT GAG CGG CTG TGT GTC AAG	504
	Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys	
	115 120 125	
55	TTC CAG TTT CTG TCC ATG CTG CAG CAT CAC CGT AAG CGG TGG CGG TTT	552
	Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe	
	130 135 140	

	TCC TTC AGC CAC TTT GTG GTA GAT CCT GGC CAG GAG TAT GAA GTG ACT S r Phe Ser His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr 145 150 155 160	600
5	GTT CAC CAC CTG CCG AAG CCC ATC CCT GAT GGG GAC CCA AAC CAC AAA Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys 165 170 175	648
10	TCC AAG ATC ATC TTT GTG CCT GAC TGT GAG GAC AGC AAG ATG AAG ATG Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met 180 185 190	696
15	ACT ACC TCA TGC GTG AGC TCA GGC AGC CTT TGG GAT CCC AAC ATC ACT Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr 195 200 205	744
20	GTG GAG ACC TTG GAC ACA CAG CAT CTG CGA GTG GAC TTC ACC CTG TGG Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp 210 215 220	792
25	AAT GAA TCC ACC CCC TAC CAG GTC CTG CTG GAA AGT TTC TCC GAC TCA Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser 225 230 235 240	840
30	GAG AAC CAC AGC TGC TTT GAT GTC GTT AAA CAA ATA TTT GCG CCC AGG Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg 245 250 255	888
35	CAA GAA GAA TTC CAT CAG CGA GCT AAT GTC ACA TTC ACT CTA AGC AAG Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys 260 265 270	936
40	TTT CAC TGG TGC TGC CAT CAC CAC GTG CAG GTC CAG CCC TTC TTC AGC Phe His Trp Cys Cys His His Val Gln Val Gln Pro Phe Phe Ser 275 280 285	984
45	AGC TGC CTA AAT GAC TGT TTG AGA CAC GCT GTG ACT GTG CCC TGC CCA Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro 290 295 300	1032
50	GTA ATC TCA AAT ACC ACA GTT CCC AAG CCA GTT GCA GAC TAC ATT CCC Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro 305 310 315 320	1080
55	CTG TGG GTG TAT GGC CTC ATC ACA CTC ATC GCC ATT CTG CTG GTG GGA Leu Trp Val Tyr Gly Leu Ile Thr Leu Ile Ala Ile Leu Val Gly 325 330 335	1128
60	TCT GTC ATC GTG CTG ATC ATC TGT ATG ACC TGG AGG CTT TCT GGC GCC Ser Val Ile Val Leu Ile Ile Cys Met Thr Trp Arg Leu Ser Gly Ala 340 345 350	1176
	GAT CAA GAG AAA CAT GGT GAT GAC TCC AAA ATC AAT GGC ATC TTG CCC Asp Gln Glu Lys His Gly Asp Asp Ser Lys Ile Asn Gly Ile Leu Pro 355 360 365	1224
	GTA GCA GAC CTG ACT CCC CCA CCC CTG AGG CCC AGG AAG GTC TGG ATC Val Ala Asp Leu Thr Pro Pro Pro Leu Arg Pro Arg Lys Val Trp Ile 370 375 380	1272

	GTC TAC TCG GCC GAC CAC CCC CTC TAT GTG GAG GTG GTC CTA AAG TTC Val Tyr S r Ala Asp His Pro Leu Tyr Val Glu Val Val Leu Lys Phe 385 390 395 400	1320
5	GCC CAG TTC CTG ATC ACT GCC TGT GGC ACT GAA GTA GCC CTT GAC CTC Ala Gln Phe Leu Ile Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu 405 410 415	1368
10	CTG GAA GAG CAG GTT ATC TCT GAG GTG GGG GTC ATG ACC TGG GTG AGC Leu Glu Glu Gln Val Ile Ser Glu Val Gly Val Met Thr Trp Val Ser 420 425 430	1416
15	CGA CAG AAG CAG GAG ATG GTG GAG AGC AAC TCC AAA ATC ATC ATC CTG Arg Gln Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Ile Leu 435 440 445	1464
20	TGT TCC CGA GGC ACC CAA GCA AAG TGG AAA GCT ATC TTG GGT TGG GCT Cys Ser Arg Gly Thr Gln Ala Lys Trp Lys Ala Ile Leu Gly Trp Ala 450 455 460	1512
25	GAG CCT GCT GTC CAG CTA CGG TGT GAC CAC TGG AAG CCT GCT GGG GAC Glu Pro Ala Val Gln Leu Arg Cys Asp His Trp Lys Pro Ala Gly Asp 465 470 475 480	1560
30	CTT TTC ACT GCA GCC ATG AAC ATG ATC CTG CCA GAC TTC AAG AGG CCA Leu Phe Thr Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro 485 490 495	1608
35	GCC TGC TTC GGC ACC TAC GTT GTT TGC TAC TTC AGT GGC ATC TGT AGT Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr Phe Ser Gly Ile Cys Ser 500 505 510	1656
40	GAG AGG GAT GTC CCC GAC CTC TTC AAC ATC ACC TCC AGG TAC CCA CTC Glu Arg Asp Val Pro Asp Leu Phe Asn Ile Thr Ser Arg Tyr Pro Leu 515 520 525	1704
45	ATG GAC AGA TTT GAG GAG GTT TAC TTC CGG ATC CAG GAC CTG GAG ATG Met Asp Arg Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met 530 535 540	1752
50	TTT GAA CCC GGC CGG ATG CAC CAT GTC AGA GAG CTC ACA GGG GAC AAT Phe Glu Pro Gly Arg Met His His Val Arg Glu Leu Thr Gly Asp Asn 545 550 555 560	1800
55	TAC CTG CAG AGC CCT AGT GGC CGG CAG CTC AAG GAG GCT GTG CTT AGG Tyr Leu Gln Ser Pro Ser Gly Arg Gln Leu Lys Glu Ala Val Leu Arg 565 570 575	1848
60	TTC CAG GAG TGG CAA ACC CAG TGC CCC GAC TGG TTC GAG CGT GAG AAC Phe Gln Glu Trp Gln Thr Gln Cys Pro Asp Trp Phe Glu Arg Glu Asn 580 585 590	1896
65	CTC TGC TTA GCT GAT GGC CAA GAT CTT CCC TCC CTG GAT GAA GAA GTG Leu Cys Leu Ala Asp Gly Gln Asp Leu Pro Ser Leu Asp Glu Glu Val 595 600 605	1944
70	TTT GAA GAC CCA CTG CTG CCA CCA GGG GGA GGA ATT GTC AAA CAG CAG Phe Glu Asp Pro Leu Leu Pro Pro Gly Gly Gly Ile Val Lys Gln Gln 610 615 620	1992

	CCC CTG GTG CGG GAA CTC CCA TCT GAC GGC TGC CTT GTG GTA GAT GTC Pro Leu Val Arg Glu Leu Pro Ser Asp Gly Cys Leu Val Val Asp Val 625 630 635 640	2040
5	TGT GTC AGT GAG GAA GAA AGT AGA ATG GCA AAG CTG GAC CCT CAG CTA Cys Val Ser Glu Glu Ser Arg Met Ala Lys Leu Asp Pro Gln Leu 645 650 655	2088
10	TGG CCA CAG AGA GAG CTA GTG GCT CAC ACC CTC CAA AGC ATG GTG CTG Trp Pro Gln Arg Glu Leu Val Ala His Thr Leu Gln Ser Met Val Leu 660 665 670	2136
15	CCA GCA GAG CAG GTC CCT GCA GCT CAT GTG GTG GAG CCT CTC CAT CTC Pro Ala Glu Gln Val Pro Ala Ala His Val Val Glu Pro Leu His Leu 675 680 685	2184
20	CCA GAC GGC AGT GGA GCA GCT GCC CAG CTG CCC ATG ACA GAG GAC AGC Pro Asp Gly Ser Gly Ala Ala Ala Gln Leu Pro Met Thr Glu Asp Ser 690 695 700	2232
25	GAG GCT TGC CCG CTG CTG GGG GTC CAG AGG AAC AGC ATC CTT TGC CTC Glu Ala Cys Pro Leu Leu Gly Val Gln Arg Asn Ser Ile Leu Cys Leu 705 710 715 720	2280
30	CCC GTG GAC TCA GAT GAC TTG CCA CTC TGT AGC ACC CCA ATG ATG TCA Pro Val Asp Ser Asp Asp Leu Pro Leu Cys Ser Thr Pro Met Met Ser 725 730 735	2328
35	CCT GAC CAC CTC CAA GGC GAT GCA AGA GAG CAG CTA GAA AGC CTA ATG Pro Asp His Leu Gln Gly Asp Ala Arg Glu Gln Leu Glu Ser Leu Met 740 745 750	2376
40	CTC TCG GTG CTG CAG CAG AGC CTG AGT GGA CAG CCC CTG GAG AGC TGG Leu Ser Val Leu Gln Gln Ser Leu Ser Gly Gln Pro Leu Glu Ser Trp 755 760 765	2424
45	CCG AGG CCA GAG GTG GTC CTC GAG GGC TGC ACA CCC TCT GAG GAG GAG Pro Arg Pro Glu Val Val Leu Glu Gly Cys Thr Pro Ser Glu Glu Glu 770 775 780	2472
50	CAG CGG CAG TCG GTG CAG TCG GAC CAG GGC TAC ATC TCC AGG AGC TCC Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser Ser 785 790 795 800	2520
55	CCG CAG CCC CCC GAG TGG CTC ACG GAG GAG GAA GAG CTA GAA CTG GGT Pro Gln Pro Pro Glu Trp Leu Thr Glu Glu Glu Leu Glu Leu Gly 805 810 815	2568
60	GAG CCC GTT GAG TCT CTC TCT CCT GAG GAA CTA CGG AGC CTG AGG AAG Glu Pro Val Glu Ser Leu Ser Pro Glu Glu Leu Arg Ser Leu Arg Lys 820 825 830	2616
	CTC CAG AGG CAG CTT TTC TTC TGG GAG CTC GAG AAG AAC CCT GGC TGG Leu Gln Arg Gln Leu Phe Phe Trp Glu Leu Glu Lys Asn Pro Gly Trp 835 840 845	2664
	AAC AGC TTG GAG CCA CGG AGA CCC ACC CCA GAA GAG CAG AAT CCC TCC Asn Ser Leu Glu Pro Arg Arg Pro Thr Pro Glu Glu Gln Asn Pro Ser 850 855 860	2712

	TAG GCCTCCTGAG CCTGCTACTT AAGAGGGTGT ATATTGTACT CTGTGTGTGC	2765
	*	
	865	
5	GTGCGTGTGT GTGTGTGTGT GTGTGTGTGT GTGCGTGTGT GTGTGTGTGT GTGTGTGTGT	2825
	GTGTGTGTAG TGCCCGGCTT AGAAATGTGA ACATCTGAAT CTGACATAGT GTTGTATAACC	2885
10	TGAAGTCCA GCACTTGGGA ACTGAGACTT GATGATCTCC TGAAGCCAGG TGTCAGGGC	2945
	CAGTGTGAAA ACATAGCAAG ACCTCAGAGA AATCAATGCA GACATCTGG TACTGATCCC	3005
	TAAACACACC CCTTTCCCTG ATAACCCGAC ATGAGCATCT GGTCATCATT GCACAAGAAT	3065
15	CCACAGCCCG TTCCCAGAGC TCATAGCAA GTGTGTTGCT CATTCTTGA ATATTTATTC	3125
	TGTACCTACT ATTCAATCAGA CATTGGAAT TCAAAACAA GTTACATGAC ACAGCCTTAG	3185
20	CCACTAAGAA GCTTAAAATT CGGTAAGGAT GTAAAATTAG CCAGGATGAA TAGAGGGCTG	3245
	CTGCCCTGGC TGCAGAAGAG CAGGTCGTCT CGTCCAGTC GAC	3288

(2) INFORMATION FOR SEQ ID NO:2:

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 865 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

35	Met Ala Ile Arg Arg Cys Trp Pro Arg Val Val Pro Gly Pro Ala Leu	
	1 5 10 15	
	Gly Trp Leu Leu Leu Leu Asn Val Leu Ala Pro Gly Arg Ala Ser	
	20 25 30	
40	Pro Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu	
	35 40 45	
	Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His	
45	50 55 60	
	Pro Lys Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu	
	65 70 75 80	
50	Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val	
	85 90 95	
	Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala	
	100 105 110	
55	Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys	
	115 120 125	
60	Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe	
	130 135 140	

S r Phe S r His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr  
 145 150 155 160

5 Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys  
 165 170 175

Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met  
 180 185 190

10 Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr  
 195 200 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp  
 15 210 215 220

Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser  
 225 230 235 240

20 Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg  
 245 250 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys  
 260 265 270

25 Phe His Trp Cys Cys His His Val Gln Val Gln Pro Phe Phe Ser  
 275 280 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro  
 30 290 295 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro  
 305 310 315 320

35 Leu Trp Val Tyr Gly Leu Ile Thr Leu Ile Ala Ile Leu Leu Val Gly  
 325 330 335

Ser Val Ile Val Leu Ile Ile Cys Met Thr Trp Arg Leu Ser Gly Ala  
 40 340 345 350

Asp Gln Glu Lys His Gly Asp Asp Ser Lys Ile Asn Gly Ile Leu Pro  
 355 360 365

Val Ala Asp Leu Thr Pro Pro Pro Leu Arg Pro Arg Lys Val Trp Ile  
 45 370 375 380

Val Tyr Ser Ala Asp His Pro Leu Tyr Val Glu Val Val Leu Lys Phe  
 385 390 395 400

50 Ala Gln Phe Leu Ile Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu  
 405 410 415

Leu Glu Glu Gln Val Ile Ser Glu Val Gly Val Met Thr Trp Val Ser  
 420 425 430

55 Arg Gln Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Ile Leu  
 435 440 445

Cys Ser Arg Gly Thr Gln Ala Lys Trp Lys Ala Ile Leu Gly Trp Ala  
 60 450 455 460

	Glu Pro Ala Val Gln Leu Arg Cys Asp His Trp Lys Pro Ala Gly Asp			
	465	470	475	480
5	Leu Phe Thr Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro			
	485	490	495	
	Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr Phe Ser Gly Ile Cys Ser			
	500	505	510	
10	Glu Arg Asp Val Pro Asp Leu Phe Asn Ile Thr Ser Arg Tyr Pro Leu			
	515	520	525	
	Met Asp Arg Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met			
15	530	535	540	
	Phe Glu Pro Gly Arg Met His His Val Arg Glu Leu Thr Gly Asp Asn			
	545	550	555	560
20	Tyr Leu Gln Ser Pro Ser Gly Arg Gln Leu Lys Glu Ala Val Leu Arg			
	565	570	575	
	Phe Gln Glu Trp Gln Thr Gln Cys Pro Asp Trp Phe Glu Arg Glu Asn			
	580	585	590	
25	Leu Cys Leu Ala Asp Gly Gln Asp Leu Pro Ser Leu Asp Glu Glu Val			
	595	600	605	
	Phe Glu Asp Pro Leu Leu Pro Pro Gly Gly Ile Val Lys Gln Gln			
30	610	615	620	
	Pro Leu Val Arg Glu Leu Pro Ser Asp Gly Cys Leu Val Val Asp Val			
	625	630	635	640
35	Cys Val Ser Glu Glu Glu Ser Arg Met Ala Lys Leu Asp Pro Gln Leu			
	645	650	655	
	Trp Pro Gln Arg Glu Leu Val Ala His Thr Leu Gln Ser Met Val Leu			
	660	665	670	
40	Pro Ala Glu Gln Val Pro Ala Ala His Val Val Glu Pro Leu His Leu			
	675	680	685	
	Pro Asp Gly Ser Gly Ala Ala Ala Gln Leu Pro Met Thr Glu Asp Ser			
45	690	695	700	
	Glu Ala Cys Pro Leu Leu Gly Val Gln Arg Asn Ser Ile Leu Cys Leu			
	705	710	715	720
50	Pro Val Asp Ser Asp Asp Leu Pro Leu Cys Ser Thr Pro Met Met Ser			
	725	730	735	
	Pro Asp His Leu Gln Gly Asp Ala Arg Glu Gln Leu Glu Ser Leu Met			
	740	745	750	
55	Leu Ser Val Leu Gln Gln Ser Leu Ser Gly Gln Pro Leu Glu Ser Trp			
	755	760	765	
60	Pro Arg Pro Glu Val Val Leu Glu Gly Cys Thr Pro Ser Glu Glu Glu			
	770	775	780	

Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser Ser  
785 790 795 800

5 Pro Gln Pro Pro Glu Trp Leu Thr Glu Glu Glu Glu Leu Glu Leu Gly  
805 810 815

Glu Pro Val Glu Ser Leu Ser Pro Glu Glu Leu Arg Ser Leu Arg Lys  
820 825 830

10 Leu Gln Arg Gln Leu Phe Phe Trp Glu Leu Glu Lys Asn Pro Gly Trp  
835 840 845

15 Asn Ser Leu Glu Pro Arg Arg Pro Thr Pro Glu Glu Gln Asn Pro Ser  
850 855 860

\*

16 865

20

## (2) INFORMATION FOR SEQ ID NO:3:

25 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 8 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: not relevant  
(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: peptide

(vii) IMMEDIATE SOURCE:  
(B) CLONE: FLAG® peptide

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Asp Tyr Lys Asp Asp Asp Asp Lys  
1 5

40

## (2) INFORMATION FOR SEQ ID NO:4:

45 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 213 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: not relevant  
(D) TOPOLOGY: linear

50 (ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:  
(A) ORGANISM: Human

55 (vii) IMMEDIATE SOURCE:  
(B) CLONE: IgG1 Fc

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Arg Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro  
 1                   5                   10                   15

5 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
 20                   25                   30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
 10                   35                   40                   45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp  
 50                   55                   60

15 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr  
 65                   70                   75                   80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp  
 20                   85                   90                   95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu  
 100                105                110

25 Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
 115                120                125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys  
 130                135                140

30 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp  
 145                150                155                160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
 165                170                175

35 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser  
 180                185                190

40 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser  
 195                200                205

Cys Ser Val Met His  
 210

45

## (2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:  
 50                   (A) LENGTH: 14 amino acids  
                       (B) TYPE: amino acid  
                       (C) STRANDEDNESS: not relevant  
                       (D) TOPOLOGY: linear

55                   (ii) MOLECULE TYPE: peptide

(vii) IMMEDIATE SOURCE:  
 55                   (B) CLONE: Polylinker

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 1                   5                   10

5

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

10                   (A) LENGTH: 498 base pairs  
                       (B) TYPE: nucleic acid  
                       (C) STRANDEDNESS: single  
                       (D) TOPOLOGY: linear

15                   (ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

20                   (iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Murine CTLA-8

25                   (ix) FEATURE:

(A) NAME/KEY: CDS  
                       (B) LOCATION: 14..490

(ix) FEATURE:

(A) NAME/KEY: sig\_peptide  
                       (B) LOCATION: 14..88

(ix) FEATURE:

(A) NAME/KEY: mat\_peptide  
                       (B) LOCATION: 89..487

35

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

40	GT CGACCCCC ACC ATG TTC CAT GTT TCT TTT AGA TAT ATC TTT GGA ATT Met Phe His Val Ser Phe Arg Tyr Ile Phe Gly Ile -25                   -20                   -15	49
45	CCT CCA CTG ATC CTT GTT CTG CTG CCT GTC ACT AGT TCT GCG GTA CTC Pro Pro Leu Ile Leu Val Leu Pro Val Thr Ser Ser Ala Val Leu -10                   -5                   1	97
50	ATC CCT CAA AGT TCA GCG TGT CCA AAC ACT GAG GCC AAG GAC TTC CTC Ile Pro Gln Ser Ser Ala Cys Pro Asn Thr Glu Ala Lys Asp Phe Leu 5                   10                   15	145
	CAG AAT GTG AAG GTC AAC CTC AAA GTC TTT AAC TCC CTT GGC GCA AAA Gln Asn Val Lys Val Asn Leu Lys Val Phe Asn Ser Leu Gly Ala Lys	193
55	20                   25                   30                   35	
	GTG AGC TCC AGA AGG CCC TCA GAC TAC CTC AAC CGT TCC ACG TCA CCC Val Ser Ser Arg Arg Pro Ser Asp Tyr Leu Asn Arg Ser Thr Ser Pro 40                   45                   50	241

	TGG ACT CTC CAC CGC AAT GAA GAC CCT GAT AGA TAT CCC TCT GTG ATC Trp Thr Leu His Arg Asn Glu Asp Pro Asp Arg Tyr Pro Ser Val Ile 55 60 65	289
5	TGG GAA GCT CAG TGC CGC CAC CAG CGC TGT GTC AAT GCG GAG GGA AAG Trp Glu Ala Gln Cys Arg His Gln Arg Cys Val Asn Ala Glu Gly Lys 70 75 80	337
10	CTG GAC CAC CAC ATG AAT TCT GTT CTC ATC CAG CAA GAG ATC CTG GTC Leu Asp His His Met Asn Ser Val Leu Ile Gln Gln Glu Ile Leu Val 85 90 95	385
15	CTG AAG AGG GAG CCT GAG AGC TGC CCC TTC ACT TTC AGG GTC GAG AAG Leu Lys Arg Glu Pro Glu Ser Cys Pro Phe Thr Phe Arg Val Glu Lys 100 105 110 115	433
20	ATG CTG GTG GGT GTG GGC TGC ACC TGC GTG GCC TCG ATT GTC CGC CAT Met Leu Val Gly Val Gly Cys Thr Cys Val Ala Ser Ile Val Arg His 120 125 130	481
	GCG TCC TAA GCGGCCGC Ala Ser *	498

25 (2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:  
 30 (A) LENGTH: 159 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

	Met Phe His Val Ser Phe Arg Tyr Ile Phe Gly Ile Pro Pro Leu Ile -25 -20 -15 -10
40	Leu Val Leu Leu Pro Val Thr Ser Ser Ala Val Leu Ile Pro Gln Ser -5 1 5
	Ser Ala Cys Pro Asn Thr Glu Ala Lys Asp Phe Leu Gln Asn Val Lys 10 15 20
45	Val Asn Leu Lys Val Phe Asn Ser Leu Gly Ala Lys Val Ser Ser Arg 25 30 35
50	Arg Pro Ser Asp Tyr Leu Asn Arg Ser Thr Ser Pro Trp Thr Leu His 40 45 50 55
	Arg Asn Glu Asp Pro Asp Arg Tyr Pro Ser Val Ile Trp Glu Ala Gln 60 65 70
55	Cys Arg His Gln Arg Cys Val Asn Ala Glu Gly Lys Leu Asp His His 75 80 85
60	Met Asn Ser Val Leu Ile Gln Gln Glu Ile Leu Val Leu Lys Arg Glu 90 95 100

	Pro	Glu	Ser	Cys	Pro	Phe	Thr	Phe	Arg	Val	Glu	Lys	Met	Leu	Val	Gly
	105							110				115				
5		Val	Gly	Cys	Thr	Cys	Val	Ala	Ser	Ile	Val	Arg	His	Ala	Ser	*
		120					125				130					

## (2) INFORMATION FOR SEQ ID NO:8:

10           (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 151 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

15           (ii) MOLECULE TYPE: protein

              (iii) HYPOTHETICAL: NO

20           (iv) ANTI-SENSE: NO

              (vi) ORIGINAL SOURCE:

- (A) ORGANISM: Herpesvirus Saimiri
- (B) CLONE: ORF13

25           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

30	Met	Thr	Phe	Arg	Met	Thr	Ser	Leu	Val	Leu	Leu	Leu	Leu	Leu	Ser	Ile
	1				5					10					15	
	Asp	Cys	Ile	Val	Lys	Ser	Glu	Ile	Thr	Ser	Ala	Gln	Thr	Pro	Arg	Cys
					20				25				30			
35	Leu	Ala	Ala	Asn	Asn	Ser	Phe	Pro	Arg	Ser	Val	Met	Val	Thr	Leu	Ser
	35						40					45				
40	Ile	Arg	Asn	Trp	Asn	Thr	Ser	Ser	Lys	Arg	Ala	Ser	Asp	Tyr	Tyr	Asn
	50						55					60				
	Arg	Ser	Thr	Ser	Pro	Trp	Thr	Leu	His	Arg	Asn	Glu	Asp	Gln	Asp	Arg
	65					70			75				80			
45	Tyr	Pro	Ser	Val	Ile	Trp	Glu	Ala	Lys	Cys	Arg	Tyr	Leu	Gly	Cys	Val
					85			90				95				
	Asn	Ala	Asp	Gly	Asn	Val	Asp	Tyr	His	Met	Asn	Ser	Val	Pro	Ile	Gln
					100				105				110			
50	Gln	Glu	Ile	Leu	Val	Val	Arg	Lys	Gly	His	Gln	Pro	Cys	Pro	Asn	Ser
					115				120			125				
55	Phe	Arg	Leu	Glu	Lys	Met	Leu	Val	Thr	Val	Gly	Cys	Thr	Cys	Val	Thr
					130			135			140					
	Pro	Ile	Val	His	Asn	Val	Asp									
					145			150								

## (2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3223 bas pairs  
 5 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA  
 10 (iii) HYPOTHETICAL: NO  
 (iv) ANTI-SENSE: NO

15 (vi) ORIGINAL SOURCE:  
 (A) ORGANISM: Human  
 (B) CLONE: IL-17R

20 (ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 93..2693

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:  
 25 GGGAGACCGG AATTCCGGGA AAAGAAAGCC TCAGAACGTT CGCTCGCTGC GTCCCCAGCC 60  
 GGGGCCGAGC CCTCCGCGAC GCCACCCGGG CC ATG GGG GCC GCA CGC AGC CCG 113  
 Met Gly Ala Ala Arg Ser Pro  
 30 1 5  
 CCG TCC GCT GTC CCG GGG CCC CTG CTG GGG CTG CTC CTG CTG CTC CTG 161  
 Pro Ser Ala Val Pro Gly Pro Leu Leu Gly Leu Leu Leu Leu Leu Leu  
 10 15 20  
 35 GGC GTG CTG GCC CCG GGT GGC GCC TCC CTG CGA CTC CTG GAC CAC CGG 209  
 Gly Val Leu Ala Pro Gly Gly Ala Ser Leu Arg Leu Leu Asp His Arg  
 25 30 35  
 40 GCG CTG GTC TGC TCC CAG CCG GGG CTA AAC TGC ACG GTC AAG AAT AGT 257  
 Ala Leu Val Cys Ser Gln Pro Gly Leu Asn Cys Thr Val Lys Asn Ser  
 40 45 50 55  
 45 ACC TGC CTG GAT GAC AGC TGG ATT CAC CCT CGA AAC CTG ACC CCC TCC 305  
 Thr Cys Leu Asp Asp Ser Trp Ile His Pro Arg Asn Leu Thr Pro Ser  
 60 65 70  
 50 TCC CCA AAG GAC CTG CAG ATC CAG CTG CAC TTT GCC CAC ACC CAA CAA 353  
 Ser Pro Lys Asp Leu Gln Ile Gln Leu His Phe Ala His Thr Gln Gln  
 75 80 85  
 GGA GAC CTG TTC CCC GTG GCT CAC ATC GAA TGG ACA CTG CAG ACA GAC 401  
 Gly Asp Leu Phe Pro Val Ala His Ile Glu Trp Thr Leu Gln Thr Asp  
 90 95 100  
 55 GCC AGC ATC CTG TAC CTC GAG GGT GCA GAG TTA TCT GTC CTG CAG CTG 449  
 Ala Ser Ile Leu Tyr Leu Glu Gly Ala Glu Leu Ser Val Leu Gln Leu  
 105 110 115

	AAC ACC AAT GAA CGT TTG TGC GTC AGG TTT GAG TTT CTG TCC AAA CTG Asn Thr Asn Glu Arg Leu Cys Val Arg Phe Glu Phe Leu S r Lys Leu 120 125 130 135	497
5	AGG CAT CAC CAC AGG CGG TGG CGT TTT ACC TTC AGC CAC TTT GTG GTT Arg His His His Arg Arg Trp Arg Ph Thr Phe Ser His Phe Val Val 140 145 150	545
10	GAC CCT GAC CAG GAA TAT GAG GTG ACC GTT CAC CAC CTG CCC AAG CCC Asp Pro Asp Gln Glu Tyr Glu Val Thr Val His His Leu Pro Lys Pro 155 160 165	593
15	ATC CCT GAT GGG GAC CCA AAC CAC CAG TCC AAG AAT TTC CTT GTG CCT Ile Pro Asp Gly Asp Pro Asn His Gln Ser Lys Asn Phe Leu Val Pro 170 175 180	641
20	GAC TGT GAG CAC GCC AGG ATG AAG GTA ACC ACG CCA TGC ATG AGC TCA Asp Cys Glu His Ala Arg Met Lys Val Thr Thr Pro Cys Met Ser Ser 185 190 195	689
25	GGC AGC CTG TGG GAC CCC AAC ATC ACC GTG GAG ACC CTG GAG GCC CAC Gly Ser Leu Trp Asp Pro Asn Ile Thr Val Glu Thr Leu Glu Ala His 200 205 210 215	737
30	CAG CTG CGT GTG AGC TTC ACC CTG TGG AAC GAA TCT ACC CAT TAC CAG Gln Leu Arg Val Ser Phe Thr Leu Trp Asn Glu Ser Thr His Tyr Gln 220 225 230	785
35	ATC CTG CTG ACC AGT TTT CCG CAC ATG GAG AAC CAC AGT TGC TTT GAG Ile Leu Leu Thr Ser Phe Pro His Met Glu Asn His Ser Cys Phe Glu 235 240 245	833
40	CAC ATG CAC CAC ATA CCT GCG CCC AGA CCA GAA GAG TTC CAC CAG CGA His Met His His Ile Pro Ala Pro Arg Pro Glu Glu Phe His Gln Arg 250 255 260	881
45	TCC AAC GTC ACA CTC ACT CTA CGC AAC CTT AAA GGG TGC TGT CGC CAC Ser Asn Val Thr Leu Thr Leu Arg Asn Leu Lys Gly Cys Cys Arg His 265 270 275	929
50	CAA GTG CAG ATC CAG CCC TTC TTC AGC AGC TGC CTC AAT GAC TGC CTC Gln Val Gln Ile Gln Pro Phe Phe Ser Ser Cys Leu Asn Asp Cys Leu 280 285 290 295	977
55	AGA CAC TCC GCG ACT GTT TCC TGC CCA GAA ATG CCA GAC ACT CCA GAA Arg His Ser Ala Thr Val Ser Cys Pro Glu Met Pro Asp Thr Pro Glu 300 305 310	1025
60	CCA ATT CCG GAC TAC ATG CCC CTG TGG GTG TAC TGG TTC ATC ACG GGC Pro Ile Pro Asp Tyr Met Pro Leu Trp Val Tyr Trp Phe Ile Thr Gly 315 320 325	1073
65	ATC TCC ATC CTG CTG GTG GGC TCC GTC ATC CTG CTC ATC GTC TGC ATG Ile Ser Ile Leu Leu Val Gly Ser Val Ile Leu Ile Val Cys Met 330 335 340	1121
70	ACC TGG AGG CTA GCT GGG CCT GGA AGT GAA AAA TAC AGT GAT GAC ACC Thr Trp Arg Leu Ala Gly Pro Gly Ser Glu Lys Tyr Ser Asp Asp Thr 345 350 355	1169

	AAA TAC ACC GAT GGC CTG CCT GCG GCT GAC CTG ATC CCC CCA CCG CTG Lys Tyr Thr Asp Gly Leu Pro Ala Ala Asp L u Ile Pro Pro Pro Leu 360 365 370 375	1217
5	AAG CCC AGG AAG GTC TGG ATC ATC TAC TCA GCC GAC CAC CCC CTC TAC Lys Pro Arg Lys Val Trp Ile Ile Tyr Ser Ala Asp His Pro Leu Tyr 380 385 390	1265
10	GTG GAC GTG GTC CTG AAA TTC GCC CAG TTC CTG CTC ACC GCC TGC GGC Val Asp Val Val Leu Lys Phe Ala Gln Phe Leu Leu Thr Ala Cys Gly 395 400 405	1313
15	ACG GAA GTG GCC CTG GAC CTG CTG GAA GAG CAG GCC ATC TCG GAG GCA Thr Glu Val Ala Leu Asp Leu Leu Glu Glu Gln Ala Ile Ser Glu Ala 410 415 420	1361
20	GGA GTC ATG ACC TGG GTG GGC CGT CAG AAG CAG GAG ATG GTG GAG AGC Gly Val Met Thr Trp Val Gly Arg Gln Lys Gln Glu Met Val Glu Ser 425 430 435	1409
25	AAC TCT AAG ATC ATC GTC CTG TGC TCC CGC GGC ACG CGC GCC AAG TGG Asn Ser Lys Ile Ile Val Leu Cys Ser Arg Gly Thr Arg Ala Lys Trp 440 445 450 455	1457
30	CAG GCG CTC CTG GGC CGG GGG GCG CCT GTG CGG CTG CGC TGC GAC CAC Gln Ala Leu Leu Gly Arg Gly Ala Pro Val Arg Leu Arg Cys Asp His 460 465 470	1505
35	GGA AAG CCC GTG GGG GAC CTG TTC ACT GCA GCC ATG AAC ATG ATC CTC Gly Lys Pro Val Gly Asp Leu Phe Thr Ala Ala Met Asn Met Ile Leu 475 480 485	1553
40	CCG GAC TTC AAG AGG CCA GCC TGC TTC GGC ACC TAC GTA GTC TGC TAC Pro Asp Phe Lys Arg Pro Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr 490 495 500	1601
45	TTC AGC GAG GTC AGC TGT GAC GGC GAC GTC CCC GAC CTG TTC GGC GCG Phe Ser Glu Val Ser Cys Asp Gly Asp Val Pro Asp Leu Phe Gly Ala 505 510 515	1649
50	GCG CCG CGG TAC CCG CTC ATG GAC AGG TTC GAG GAG GTG TAC TTC CGC Ala Pro Arg Tyr Pro Leu Met Asp Arg Phe Glu Val Tyr Phe Arg 520 525 530 535	1697
55	ATC CAG GAC CTG GAG ATG TTC CAG CCG GGC CGC ATG CAC CGC GTA GGG Ile Gln Asp Leu Glu Met Phe Gln Pro Gly Arg Met His Arg Val Gly 540 545 550 555	1745
60	GAG CTG TCG GGG GAC AAC TAC CTG CGG AGC CCG GGC GGC AGG CAG CTC Glu Leu Ser Gly Asp Asn Tyr Leu Arg Ser Pro Gly Gly Arg Gln Leu 555 560 565	1793
65	CGC GCC CTG GAC AGG TTC CGG GAC TGG CAG GTC CGC TGT CCC GAC Arg Ala Ala Leu Asp Arg Phe Arg Asp Trp Gln Val Arg Cys Pro Asp 570 575 580	1841
70	TGG TTC GAA TGT GAG AAC CTC TAC TCA GCA GAT GAC CAG GAT GCC CCG Trp Phe Glu Cys Glu Asn Leu Tyr Ser Ala Asp Asp Gln Asp Ala Pro 585 590 595	1889

	TCC CTG GAC GAA GAG GTG TTT GAG GAG CCA CTG CTG CCT CCG GGA ACC Ser Leu Asp Glu Glu Val Phe Glu Glu Pro Leu Leu Pro Pro Gly Thr 600 605 610 615	1937
5	GGC ATC GTG AAG CGG GCG CCC CTG GTG CGC GAG CCT GGC TCC CAG GCC Gly Ile Val Lys Arg Ala Pro Leu Val Arg Glu Pro Gly Ser Gln Ala 620 625 630	1985
10	TGC CTG GCC ATA GAC CCG CTG GTC GGG GAG GAA GGA GGA GCA GCA GTG Cys Leu Ala Ile Asp Pro Leu Val Gly Glu Glu Gly Gly Ala Ala Val 635 640 645	2033
15	GCA AAG CTG GAA CCT CAC CTG CAG CCC CGG GGT CAG CCA GCG CCG CAG Ala Lys Leu Glu Pro His Leu Gln Pro Arg Gly Gln Pro Ala Pro Gln 650 655 660	2081
20	CCC CTC CAC ACC CTG GTG CTC GCC GCA GAG GAG GGG GCC CTG GTG GCC Pro Leu His Thr Leu Val Leu Ala Ala Glu Glu Gly Ala Leu Val Ala 665 670 675	2129
25	GCG GTG GAG CCT GGG CCC CTG GCT GAC GGT GCC GCA GTC CGG CTG GCA Ala Val Glu Pro Gly Pro Leu Ala Asp Gly Ala Ala Val Arg Leu Ala 680 685 690 695	2177
30	CTG GCG GGG GAG GGC GAG GCC TGC CCG CTG CTG GGC AGC CCG GGC GCT Leu Ala Gly Glu Gly Ala Cys Pro Leu Leu Gly Ser Pro Gly Ala 700 705 710	2225
35	GGG CGA AAT AGC GTC CTC TTC CTC CCC GTG GAC CCC GAG GAC TCG CCC Gly Arg Asn Ser Val Leu Phe Leu Pro Val Asp Pro Glu Asp Ser Pro 715 720 725	2273
40	CTT GGC AGC AGC ACC CCC ATG GCG TCT CCT GAC CTC CTT CCA GAG GAC Leu Gly Ser Ser Thr Pro Met Ala Ser Pro Asp Leu Leu Pro Glu Asp 730 735 740	2321
45	GTG AGG GAG CAC CTC GAA GGC TTG ATG CTC TCG CTC TTC GAG CAG AGT Val Arg Glu His Leu Glu Gly Leu Met Leu Ser Leu Phe Glu Gln Ser 745 750 755	2369
50	CTG AGC TGC CAG GCC CAG GGG GGC TGC AGT AGA CCC GCC ATG GTC CTC Leu Ser Cys Gln Ala Gln Gly Gly Cys Ser Arg Pro Ala Met Val Leu 760 765 770 775	2417
55	ACA GAC CCA CAC ACG CCC TAC GAG GAG GAG CAG CGG CAG TCA GTG CAG Thr Asp Pro His Thr Pro Tyr Glu Glu Glu Gln Arg Gln Ser Val Gln 780 785 790	2465
60	TCT GAC CAG GGC TAC ATC TCC AGG AGC TCC CCG CAG CCC CCC GAG GGA Ser Asp Gln Gly Tyr Ile Ser Arg Ser Ser Pro Gln Pro Pro Glu Gly 795 800 805	2513
	CTC ACG GAA ATG GAG GAA GAG GAG GAA GAG GAG CAG GAC CCA GGG AAG Leu Thr Glu Met Glu Glu Glu Glu Glu Gln Asp Pro Gly Lys 810 815 820	2561
	CCG GCC CTG CCA CTC TCT CCC GAG GAC CTG GAG AGC CTG AGG AGC CTC Pro Ala Leu Pro Leu Ser Pro Glu Asp Leu Glu Ser Leu Arg Ser Leu 825 830 835	2609

	CAG CGG CAG CTG CTT TTC CGC CAG CTG CAG AAG AAC TCG GGC TGG GAC Gln Arg Gln Leu Leu Phe Arg Gln Leu Gln Lys Asn Ser Gly Trp Asp 840                    845                    850                    855	2657
5	ACG ATG GGG TCA GAG TCA GAG GGG CCC AGT GCA TGA GGGCGGCTCC Thr Met Gly Ser Glu Ser Glu Gly Pro Ser Ala * 860                    865	2703
10	CCAGGGACCG CCCAGATCCC AGCTTGAGA GAGGAGTGTG TGTGCACGTA TTCACTGTG TGTACATGTC TGCATGTGTA TATGTTCGTG TGTGAAATGT AGGCTTAAA ATGTAATGT CTGGATTTA ATCCCAGGCA TCCCTCCTAA CTTTCTTG TGCAGCGGTC TGGTTATCGT	2763                2823                2883
15	CTATCCCCAG GGGATCCAC ACAGCCCCCT CCCAGGAGCT AATGGTAGAG CGTCCTTGAG GCTCCATTAT TCGTCATTAC AGCATTATT GTGCACCTAC TATGTGGCGG GCATTTGGGA	2943                3003
20	TACCAAGATA AATTGCATGC GGCAATGGCCC CAGCCATGAA GGAACTTAAC CGCTAGTGCC GAGGACACGT TAAACGAACA GGATGGGCCG GGCACGGTGG CTCACGCCCTG TAATCCCAGC ACACTGGGAG GCCGAGGCAG GTGGATCACT CTGAGGTCAG GAGTTGAGC CAGCCTGGCC	3063                3123                3183
25	AACATGGTGA AACCCCGGAA TTCGAGCTCG GTACCCGGGG	3223

## (2) INFORMATION FOR SEQ ID NO:10:

30	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 867 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear
35	(ii) MOLECULE TYPE: protein
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
40	Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu 1                    5                    10                    15
	Gly Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser 20                  25                  30
45	Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu 35                  40                  45
	Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His 50                  55                  60
50	Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu 65                  70                  75                  80
	His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile 85                  90                  95
55	Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala 100                105                110

	Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg L u Cys Val Arg			
	115	120	125	
5	Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe			
	130	135	140	
	Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr			
	145	150	155	160
10	Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln			
	165	170	175	
15	Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val			
	180	185	190	
	Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr			
	195	200	205	
20	Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp			
	210	215	220	
	Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met			
	225	230	235	240
25	Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg			
	245	250	255	
30	Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn			
	260	265	270	
	Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser			
	275	280	285	
35	Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro			
	290	295	300	
	Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp			
	305	310	315	320
40	Val Tyr Trp Phe Ile Thr Gly Ile Ser Ile Leu Leu Val Gly Ser Val			
	325	330	335	
45	Ile Leu Leu Ile Val Cys Met Thr Trp Arg Leu Ala Gly Pro Gly Ser			
	340	345	350	
	Glu Lys Tyr Ser Asp Asp Thr Lys Tyr Thr Asp Gly Leu Pro Ala Ala			
	355	360	365	
50	Asp Leu Ile Pro Pro Pro Leu Lys Pro Arg Lys Val Trp Ile Ile Tyr			
	370	375	380	
	Ser Ala Asp His Pro Leu Tyr Val Asp Val Val Leu Lys Phe Ala Gln			
	385	390	395	400
55	Phe Leu Leu Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu Leu Glu			
	405	410	415	
60	Glu Gln Ala Ile Ser Glu Ala Gly Val Met Thr Trp Val Gly Arg Gln			
	420	425	430	

Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Val Leu Cys Ser  
 435 440 445  
 Arg Gly Thr Arg Ala Lys Trp Gln Ala Leu Leu Gly Arg Gly Ala Pro  
 5 450 455 460  
 Val Arg Leu Arg Cys Asp His Gly Lys Pro Val Gly Asp Leu Phe Thr  
 465 470 475 480  
 10 Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro Ala Cys Phe  
 485 490 495  
 Gly Thr Tyr Val Val Cys Tyr Phe Ser Glu Val Ser Cys Asp Gly Asp  
 15 500 505 510  
 Val Pro Asp Leu Phe Gly Ala Ala Pro Arg Tyr Pro Leu Met Asp Arg  
 515 520 525  
 20 Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met Phe Gln Pro  
 530 535 540  
 Gly Arg Met His Arg Val Gly Glu Leu Ser Gly Asp Asn Tyr Leu Arg  
 545 550 555 560  
 25 Ser Pro Gly Gly Arg Gln Leu Arg Ala Ala Leu Asp Arg Phe Arg Asp  
 565 570 575  
 Trp Gln Val Arg Cys Pro Asp Trp Phe Glu Cys Glu Asn Leu Tyr Ser  
 30 580 585 590  
 Ala Asp Asp Gln Asp Ala Pro Ser Leu Asp Glu Glu Val Phe Glu Glu  
 595 600 605  
 35 Pro Leu Leu Pro Pro Gly Thr Gly Ile Val Lys Arg Ala Pro Leu Val  
 610 615 620  
 Arg Glu Pro Gly Ser Gln Ala Cys Leu Ala Ile Asp Pro Leu Val Gly  
 625 630 635 640  
 40 Glu Glu Gly Ala Ala Val Ala Lys Leu Glu Pro His Leu Gln Pro  
 645 650 655  
 Arg Gly Gln Pro Ala Pro Gln Pro Leu His Thr Leu Val Leu Ala Ala  
 45 660 665 670  
 Glu Glu Gly Ala Leu Val Ala Ala Val Glu Pro Gly Pro Leu Ala Asp  
 675 680 685  
 50 Gly Ala Ala Val Arg Leu Ala Leu Ala Gly Glu Gly Glu Ala Cys Pro  
 690 695 700  
 Leu Leu Gly Ser Pro Gly Ala Gly Arg Asn Ser Val Leu Phe Leu Pro  
 705 710 715 720  
 55 Val Asp Pro Glu Asp Ser Pro Leu Gly Ser Ser Thr Pro Met Ala Ser  
 725 730 735  
 Pro Asp Leu Leu Pro Glu Asp Val Arg Glu His Leu Glu Gly Leu Met  
 60 740 745 750

Leu Ser Leu Phe Glu Gln Ser Leu Ser Cys Gln Ala Gln Gly Gly Cys  
755 760 765

5 Ser Arg Pro Ala Met Val Leu Thr Asp Pro His Thr Pro Tyr Glu Glu  
770 775 780

Glu Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser  
785 790 795 800

10 Ser Pro Gln Pro Pro Glu Gly Leu Thr Glu Met Glu Glu Glu Glu  
805 810 815

Glu Glu Gln Asp Pro Gly Lys Pro Ala Leu Pro Leu Ser Pro Glu Asp  
820 825 830

15 Leu Glu Ser Leu Arg Ser Leu Gln Arg Gln Leu Leu Phe Arg Gln Leu  
835 840 845

20 Gln Lys Asn Ser Gly Trp Asp Thr Met Gly Ser Glu Ser Glu Gly Pro  
850 855 860

Ser Ala \*

25

CLAIMS

We claim:

1. An isolated DNA selected from the group consisting of:
  - 5 (a) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;
  - (b) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10; and
  - (c) DNA molecules capable of hybridization to the DNA of (a) or (b) under 10 stringent conditions, and which encode IL-17R that bind IL-17; and
  - (d) DNA molecules encoding fragments of proteins encoded by the DNA of (a), (b), or (c), which fragments bind IL-17.
2. An isolated oligonucleotide that is a fragment of a DNA according to claim 1, 15 selected from the group consisting of oligonucleotides of at least about 17 nucleotides in length, oligonucleotides of at least about 25 nucleotides in length, and oligonucleotides of at least about 30 nucleotides in length.
3. An isolated DNA selected from the group consisting of:
  - 20 (a) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;
  - (b) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10;
  - (c) DNA molecules encoding proteins that are at least about 70% identical in 25 amino acid sequence to the proteins of (a) or (b), and that bind IL-17; and
  - (d) DNA molecules encoding fragments of proteins encoded by the DNA of (a), (b), or (c), which fragments bind IL-17.
4. A recombinant expression vector comprising a DNA sequence according to claim 1. 30
5. A recombinant expression vector according to claim 4 that expresses a soluble IL-17R.
6. A recombinant expression vector comprising a DNA sequence according to claim 3. 35
7. A host cell transformed or transfected with an expression vector according to claim 4.

8. A host cell transformed or transfected with an expression vector according to claim 5.
- 5        9. A host cell transformed or transfected with an expression vector according to claim 6.
- 10      10. A process for preparing an IL-17R protein, comprising culturing a host cell according to claim 7 under conditions promoting expression and recovering the IL-17R.
- 15      11. A process for preparing an IL-17R protein, comprising culturing a host cell according to claim 8 under conditions promoting expression and recovering the IL-17R.
13. An isolated and purified Interleukin-17 receptor (IL-17R) protein that binds IL-17, selected from the group consisting of
  - (a) a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;
  - (b) a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10;
  - (c) proteins encoded by DNA molecules capable of hybridization to DNA's encoding the proteins of (a) or (b) under stringent conditions, and which bind IL-17; and
  - (d) fragments of the proteins of (a), (b), or (c), that bind IL-17.
14. An isolated and purified IL-17R protein, selected from the group consisting of:
  - (a) a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;
  - (b) a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10;
  - (c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b), and that binds IL-17; and
  - (d) fragments of the proteins of (a), (b), or (c), that bind IL-17.
- 35      15. An isolated and purified IL-17R according to claim 14, consisting essentially of soluble IL-17R.

16. A composition comprising an IL-17R protein according to claim 13, and a suitable diluent or carrier.
- 5        17. A method for regulating an immune or inflammatory response in a mammal, comprising administering an effective amount of a composition according to claim 16.
- 10      18. An assay kit for detection of IL-17, IL-17R, the interaction of IL-17 and IL-17R, or antagonists or mimetics of the interaction, comprising a protein composition according to claim 16, and a detecting reagent.
19. An antibody immunoreactive with IL-17R.
20. The antibody of claim 19 which is a monoclonal antibody.
- 15      21. A method for suppressing rejection of a grafted organ or grafted tissue in a graft recipient, comprising administering an effective amount of a composition according to claim 16 to the recipient.
- 20      22. A method for suppressing rejection of a grafted organ or grafted tissue in a graft recipient, comprising transfecting the organ or tissue to be transplanted with a DNA encoding a soluble IL-17R according to claim 1, and engrafting the organ or tissue in the recipient.
23. The method according to claim 22, further comprising administering a composition according to claim 16 to the recipient.
- 25      24. The use of an IL-17R protein according to claim 13 or 14 for preparation of a composition for suppressing rejection of a grafted organ or grafted tissue in a graft recipient.
- 25      25. The use of a DNA encoding a soluble IL-17R according to claim 1 or 3 for preparation of a composition for suppressing rejection of a grafted organ or grafted tissue in a graft recipient.
- 30      26. The use of a DNA encoding a soluble IL-17R according to claim 1 or 3 and an IL-17R protein according to claim 13 or 14, for preparation of a composition or compositions for separate, simultaneous or sequential administration for suppressing rejection of a grafted organ or grafted tissue in a graft recipient.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/04018

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C12N15/12	C12N15/85	C12N5/10	C07K14/715	A61K38/17
	G01N33/68	C07K16/28	A61K48/00	//C12N15/62, C07K19/00	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SCIENCE, vol. 248, no. 4950, 11 May 1990, WASHINGTON, DC, USA, pages 739-742, XP002010936 W. FANSLOW ET AL.: "Regulation of alloreactivity in vivo by a soluble form of the interleukin-1 receptor." see abstract</p> <p>---</p> <p>THE JOURNAL OF IMMUNOLOGY, vol. 147, no. 2, 15 July 1991, BALTIMORE, MD, USA, pages 535-540, XP002010937 W. FANSLOW ET AL.: "Regulation of alloreactivity in vivo by IL-4 and the soluble IL-4 receptor." see abstract</p> <p>---</p> <p>-/-</p>	13-17, 21,24
A		13-17, 21,24

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

14 August 1996

Date of mailing of the international search report

22.08.96

Name and mailing address of the ISA

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Authorized officer

Nooij, F

## INTERNATIONAL SEARCH REPORT

International Application No PCT/US 96/04018
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	IMMUNITY, vol. 3, no. 6, December 1995, USA, pages 811-821, XP000578349 Z. YAO ET AL.: "Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor." see the whole document ---	1-19
P,X	WO,A,95 18826 (SCHERING CORP. & INSERM) 13 July 1995 see claims 14-17 -----	13-15

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US 96/04018

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 17, 21-23  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Although these claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No  
PCT/US 96/04018

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9518826	13-07-95	AU-B- 1520895	01-08-95